LYOPHILIZED THERAPEUTIC PEPTIBODY FORMULATIONS

FIELD OF THE INVENTION

[0001] Generally, the invention relates to formulations of lyophilized therapeutic peptibodies and methods for making a lyophilized composition comprising therapeutic peptibodies.

BACKGROUND OF THE INVENTION

[0002] Recombinant proteins are an emerging class of therapeutic agents. Such recombinant therapeutics have engendered advances in protein formulation and chemical modification. Modifications have been identified that can protect therapeutic proteins, primarily by blocking their exposure to proteolytic enzymes. Protein modifications may also increase the therapeutic protein's stability, circulation time, and biological activity. A review article describing protein modification and fusion proteins is Francis (1992), Focus on Growth Factors 3:4-10 (Mediscript, London), which is hereby incorporated by reference.

[0003] One useful modification is combination of a polypeptide with an "Fc" 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. See also, e.g., U.S. Patent No. 5,428,130. When constructed together with a therapeutic peptibody or 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 fusions with therapeutic proteins known in the art.

Table 1—Fc fusion with therapeutic proteins

Form of Fc	Fusion partner	Therapeutic implications	Reference
IgG1	N-terminus of CD30-L	Hodgkin's disease; anaplastic lymphoma; T-cell leukemia	U.S. Patent No. 5,480,981
Murine Fcγ2a	IL-10	anti-inflammatory; transplant rejection	Zheng et al. (1995), J. Immunol. 154: 5590-600
IgG1	TNF receptor	septic shock	Fisher et al. (1996), N. Engl. J. Med. 334: 1697-1702; Van Zee, K. et al. (1996), J. Immunol. 156: 2221-30
IgG, IgA, IgM, or IgE (excluding the first domain)	TNF receptor	inflammation, autoimmune disorders	U.S. Pat. No. 5,808,029, issued September 15, 1998
IgG1	CD4 receptor	AIDS	Capon et al. (1989), Nature 337: 525-31
IgG1, IgG3	N-terminus of IL-2	anti-cancer, antiviral	Harvill et al. (1995), Immunotech. 1: 95-105
IgG1	C-terminus of OPG	osteoarthritis; bone density	WO 97/23614, published July 3, 1997
IgG1	N-terminus of leptin	anti-obesity	PCT/US 97/23183, filed December 11, 1997
Human Ig Cγ1	CTLA-4	autoimmune disorders	Linsley (1991), J. Exp. Med. 174:561-9

[0004] Polyethylene glycol ("PEG") conjugated or fusion proteins and peptides have also been studied for use in pharmaceuticals, on artificial implants, and other applications where biocompatibility is of importance. Various derivatives of PEG have been proposed that have an active moiety for permitting PEG to be attached to pharmaceuticals and implants and to molecules and surfaces generally. For example, PEG derivatives have been proposed for coupling PEG to surfaces to control wetting, static buildup, and attachment of other types of molecules to the surface, including proteins or protein residues.

[0005] In other studies, coupling of PEG ("PEGylation") has been shown to be desirable in overcoming obstacles encountered in clinical use of biologically active molecules. Published

PCT Publication No. WO 92/16221 states, for example, that many potentially therapeutic proteins have been found to have a short half life in blood serum.

[0006] PEGylation decreases the rate of clearance from the bloodstream by increasing the apparent molecular weight of the molecule. Up to a certain size, the rate of glomerular filtration of proteins is inversely proportional to the size of the protein. The ability of PEGylation to decrease clearance, therefore, is generally not a function of how many PEG groups are attached to the protein, but the overall molecular weight of the conjugated protein. Decreased clearance can lead to increased efficacy over the non-PEGylated material. See, for example, Conforti et al., Pharm. Research Commun. vol. 19, pg. 287 (1987) and Katre et., Proc. Natl. Acad. Sci. U.S.A. vol. 84, pg. 1487 (1987).

[0007] In addition, PEGylation can decrease protein aggregation, (Suzuki et al., Biochem. Biophys. Acta vol. 788, pg. 248 (1984)), alter (i.e.,) protein immunogenicity (Abuchowski et al., J. Biol. Chem. vol. 252 pg. 3582 (1977)), and increase protein solubility as described, for example, in PCT Publication No. WO 92/16221.

[0008] In general, the interaction of a protein ligand with its receptor often takes place at a relatively large interface. However, as demonstrated in the case of human growth hormone bound to its receptor, only a few key residues at the interface actually contribute to most of the binding energy. Clackson, T. et al., Science 267:383-386 (1995). This observation and the fact that the bulk of the remaining protein ligand serves only to display the binding epitopes in the right topology makes it possible to find active ligands of much smaller size. Thus, molecules of only "peptide" length as defined herein 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").

[0009] 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 Jun. 29, 1993; U.S. Pat. No. 5,733,731, issued Mar. 31, 1998; U.S. Pat. No. 5,498,530, issued Mar. 12, 1996; U.S. Pat. No. 5,432,018, issued Jul. 11, 1995; U.S. Pat. No. 5,338,665, issued Aug. 16, 1994; U.S. Pat. No. 5,922,545, issued Jul. 13, 1999; WO 96/40987, published Dec. 19, 1996; and WO 98/15833, published Apr. 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, and the best binding peptides are 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.

[0010] Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor 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). 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 Smith et al. (1993), Mol. Pharmacol. 43: 741-8. 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. This and related methods are collectively 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. This and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized 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. These and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be 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.

[0011] In the case of known bioactive peptides, rational design of peptide ligands with favorable therapeutic properties can be carried out. In such an approach, stepwise changes are made to a peptide sequence and the effect of the substitution upon bioactivity or a predictive biophysical property of the peptide (e.g., solution structure) is determined. These techniques are collectively referred to as "rational design." In one such technique, a series of peptides is made in which a single residue at a time is replaced 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.

[0012] 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. 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.

[0013] Conceptually, peptide mimetics of any protein can be identified using phage display and the other methods mentioned above. These methods have also 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.

[0014] Of particular interest 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 therefor 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[1]	Pharmacologic activity	Reference
intrapeptide disulfide-bonded	EPO receptor	EPO-mimetic	Wrighton et al. (1996), Science 273: 458-63; U.S. Pat. No. 5,773,569, issued June 30, 1998 to Wrighton et al.
C-terminally cross-linked dimer	EPO receptor	EPO-mimetic	Livnah et al. (1996), Science 273: 464-71; Wrighton et al. (1997), Nature Biotechnology 15: 1261-5; International patent application WO 96/40772, published Dec. 19, 1996
linear	EPO receptor	EPO-mimetic	Naranda et al. (1999), Proc. Natl. Acad. Sci. USA, 96: 7569-74; WO 99/47151, published September 23, 1999
linear	c-Mpl	TPO-mimetic	Cwirla et al.(1997) Science 276: 1696-9; U.S. Pat. No. 5,869,451, issued Feb. 9, 1999; U.S. Pat. No. 5,932,946, issued Aug. 3, 1999
C-terminally cross-linked dimer	c-Mpl	TPO-mimetic	Cwirla et al. (1997), Science 276: 1696-9
disulfide-linked dimer		stimulation of hematopoiesis ("G-CSF-mimetic")	Paukovits et al. (1984), Hoppe-Seylers Z. Physiol. Chem. 365: 303-11; Laerum et al. (1988), Exp. Hemat. 16: 274-80

[1] 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.

alkylene-linked dimer		G-CSF-mimetic	Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9; Cuthbertson et al. (1997), J. Med. Chem. 40: 2876-82; King et al. (1991), Exp. Hematol. 19:481; King et al. (1995), Blood 86 (Suppl. 1): 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 et al. (1996), Proc. Natl. Acad. Sci. 93: 7381-6; Akeson et al. (1996), J. Biol. Chem. 271: 30517-23; Wiekzorek et al. (1997), Pol. J. Pharmacol. 49: 107-17; Yanofsky (1996), PNAs, 93:7381-7386.
linear	Facteur thymique serique (FTS)	stimulation of lymphocytes ("FTS-mimetic")	Inagaki-Ohara et al. (1996), Cellular Immunol. 171: 30-40; Yoshida (1984), Int. J. Immunopharmacol, 6:141-6.
intrapeptide disulfide bonded	CTLA4 MAb	CTLA4-mimetic	Fukumoto et al. (1998), Nature Biotech. 16: 267-70
exocyclic	TNF-α receptor	TNF-α antagonist	Takasaki et al. (1997), Nature Biotech. 15:1266-70; WO 98/53842, published December 3, 1998
linear	TNF-α receptor	TNF-α antagonist	Chirinos-Rojas (1998), J. Imm., 5621-5626.
intrapeptide disulfide bonded	C3b	inhibition of complement activation; autoimmune diseases ("C3b-antagonist")	Sahu et al. (1996), J. Immunol. 157: 884-91; Morikis et al. (1998), Protein Sci. 7: 619-27
linear	vinculin	cell adhesion processes—	Adey et al. (1997),

		cell growth, differentiation, wound healing, tumor metastasis ("vinculin binding")	Biochem. J. 324: 523-8
linear	C4 binding protein (C4BP)	anti-thrombotic	Linse et al. (1997), J. Biol. Chem. 272: 14658-65
linear	urokinase receptor	processes associated with urokinase interaction with its receptor (e.g., angiogenesis, tumor cell invasion and metastasis); ("UKR antagonist")	Goodson et al. (1994), Proc. Natl. Acad. Sci. 91: 7129-33; International application WO 97/35969, published October 2, 1997
linear	Mdm2, Hdm2	Inhibition of inactivation of p53 mediated by Mdm2 or hdm2; anti-tumor ("Mdm/hdm antagonist")	Picksley et al. (1994), Oncogene 9: 2523-9; Bottger et al. (1997) J. Mol. Biol. 269: 744-56; Bottger et al. (1996), Oncogene 13: 2141-7
linear	$p21^{WAF1}$	anti-tumor by mimicking the activity of $p21^{WAF1}$	Ball et al. (1997), Curr. Biol. 7: 71-80
linear	farnesyl transferase	anti-cancer by preventing activation of ras oncogene	Gibbs et al. (1994), Cell 77:175-178
linear	Ras effector domain	anti-cancer by inhibiting biological function of the ras oncogene	Moodie et al. (1994), Trends Genet 10: 44-48 Rodriguez et al. (1994), Nature 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 et al (1993), Curr. Biol. 3:434-432 Yu et al. (1994), Cell 76:933-945; Rickles et al. (1994), EMBO J. 13: 5598-5604; Sparks et al. (1994), J. Biol. Chem. 269: 23853-6; Sparks et al. (1996), Proc. Natl. Acad. Sci. 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")	Fåhraeus et al. (1996), Curr. Biol. 6:84-91
linear	Src, Lyn	inhibition of Mast cell activation, IgE-related conditions, type I hypersensitivity ("Mast cell antagonist")	Stauffer et al. (1997), Biochem. 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), Proc. Natl. Acad. Sci. 92: 2194-8
linear	selectins	neutrophil adhesion; inflammatory diseases ("selectin antagonist")	Martens et al. (1995), J. Biol. Chem. 270: 21129-36; European patent application EP 0 714 912, published June 5, 1996
linear, cyclized	calmodulin	calmodulin antagonist	Pierce et al. (1995), Molec. Diversity 1: 259-65; Dedman et al. (1993), J. Biol. Chem. 268: 23025-30; Adey & Kay (1996), Gene 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), J. Biol. Chem. 274: 1979-1985
cyclic, linear	fibronectin and	treatment of inflammatory	WO 98/09985, published

	extracellular matrix components of T cells and macrophages	and autoimmune conditions	March 12, 1998
linear	somatostatin and cortistatin	treatment or prevention of hormone-producing tumors, acromegaly, giantism, dementia, gastric ulcer, tumor growth, inhibition of hormone secretion, modulation of sleep or neural activity	European patent application 0 911 393, published April 28, 1999
linear	bacterial lipopolysac-charide	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), Biochem., 27:4066-71.
linear	Amylin		Cooper (1987), Proc. Natl. Acad. Sci., 84:8628-32.
linear	Adrenomedullin		Kitamura (1993), BBRC, 192:553-60.
cyclic, linear	VEGF	anti-angiogenic; cancer, rheumatoid arthritis, diabetic retinopathy, psoriasis ("VEGF antagonist")	Fairbrother (1998), Biochem., 37:17754-17764.
cyclic	MMP	inflammation and autoimmune disorders; tumor growth ("MMP inhibitor")	Koivunen (1999), Nature Biotech., 17:768-774.
	HGH fragment	treatment of obesity	U.S. Pat. No. 5,869,452

	Echistatin	inhibition of platelet aggregation	Gan (1988), J. Biol. Chem., 263:19827-32.
linear	SLE autoantibody	SLE	WO 96/30057, published October 3, 1996
	GD1alpha	suppression of tumor metastasis	Ishikawa et al. (1998), FEBS Lett. 441 (1): 20-4
	antiphospholipid beta-2-glycoprotein-I (β2GPI) antibodies	endothelial cell activation , antiphospholipid syndrome (APS), thromboembolic phenomena, thrombocytopenia, and recurrent fetal loss	Blank et al. (1999), Proc. Natl. Acad. Sci. USA 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), Peptides 7:1165.
linear	C-Reactive	inflammation and cancer	Barna (1994), Cancer

	Protein (CRP)		Immunol. Immunother. 38:38 (1994).
linear	Sperm-Activating Peptides	infertility	Suzuki (1992), Comp. Biochem. Physiol. 102B:679.
linear	angiotensins	hematopoietic factors for hematocytopenic conditions from cancer, AIDS, etc.	Lundergan (1999), J. Periodontal Res. 34(4):223-228.
linear	HIV-1 gp41	anti-AIDS	Chan (1998), Cell 93:681-684.
linear	PKC	inhibition of bone resorption	Moonga (1998), Exp. Physiol. 83:717-725.
linear	defensins (HNP-1, -2, -3, -4)	antimicrobial	Harvig (1994), Methods Enz. 236:160-172.
linear	$p185^{HER2/neu}$, C-erbB-2	AHNP-mimetic:anti-tumor	Park (2000), Nat. Biotechnol. 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.

[0015] Peptides identified by peptide library screening have been regarded as "leads" in development of therapeutic agents rather than being used 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 presently uses 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. Lowman (1997), Ann. Rev. Biophys. Biomol. Struct. 26: 401-24; Kay et al. (1998), Drug Disc. Today 3: 370-8.

[0016] Typically, purified peptides are only marginally stable in an aqueous state and undergo chemical and physical degradation resulting in a loss of biological activity during processing and storage. Additionally, peptide compositions in aqueous solution undergo hydrolysis, such as deamidation and peptide bond cleavage. These effects represent a serious problem for therapeutically active peptides which are intended to be administered to humans within a defined dosage range based on biological activity.

[0017] Administration of purified peptides remains a promising treatment strategy for many diseases that affect the human population. However, the ability of the therapeutic peptibody to remain a stable pharmaceutical composition over time in a variety of storage conditions and then be effective for patients *in vivo* has not been addressed. Thus, there remains a need in the art to provide therapeutic peptibodies in stable formulations that are useful as therapeutic agents for the treatment of diseases and disorders.

SUMMARY OF THE INVENTION

[0018] The present invention provides formulations useful for lyophilization of therapeutic peptibodies, resulting in a highly stable therapeutic peptibody product. The stable therapeutic peptibody product is useful as a therapeutic agent in the treatment of individuals suffering from disorders or conditions that can benefit from the administration of the therapeutic peptibody.

[0019] In one aspect, the invention provides a lyophilized therapeutic peptibody composition comprising a buffer, a bulking agent, a stabilizing agent, and optionally a surfactant; wherein the buffer is comprised of a pH buffering agent in a range of about 5 mM to about 20 mM and wherein the pH is in a range of about 3.0 to about 8.0; wherein the bulking agent is at a concentration of about 0% to about 4.5% w/v; wherein the stabilizing agent is at a concentration of about 0.1% to about 20% w/v; wherein the surfactant is at a concentration of about 0.004% to about 0.4% w/v; and wherein the therapeutic peptibody comprises a structure set out in Formula I,

Formula I: $[(X^1)_a\text{-}F^1\text{-}(X^2)_b]\text{-}(L^1)_c\text{-}WSP_d$

wherein:

F^1 is an Fc domain;

X^1 is selected from

$P^1\text{-}(L^2)_e\text{-}$

P^2-$(L^3)_f$-P^1-$(L^2)_e$-

P^3-$(L^4)_g$-P^2-$(L^3)_f$-P^1-$(L^2)_e$- and

P^4-$(L^5)_h$-P^3-$(L^4)_g$-P^2-$(L^3)_f$-P^1-$(L^2)_e$-

X^2 is selected from:

-$(L^2)_e$-P^1,

-$(L^2)_e$-P^1-$(L^3)_f$-P^2,

-$(L^2)_e$-P^1-$(L^3)_f$-P^2-$(L^4)_g$-P^3, and

-$(L^2)_e$-P^1-$(L^3)_f$-P^2-$(L^4)_g$-P^3-$(L^5)_h$-P^4

wherein P^1, P^2, P^3, and P^4 are each independently sequences of pharmacologically active peptides;

L^1, L^2, L^3, L^4, and L^5 are each independently linkers;

a, b, c, e, f, g, and h are each independently 0 or 1,

provided that at least one of a and b is 1;

d is 0, 1, or greater than 1; and

WSP is a water soluble polymer, the attachment of which is effected at any reactive moiety in F^1.

[0020] In another embodiment, the therapeutic peptibody comprises a structure set out in Formula II

Formula II: $[X^1\text{-}F^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the C-terminus of X^1, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0021] In still another embodiment, the therapeutic peptibody comprises a structure set out in Formula III

Formula III: $[F^1\text{-}X^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of X^2, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0022] In yet another embodiment, the therapeutic peptibody comprises a structure set out in Formula IV

Formula IV: $[F^1\text{-}(L^1)_e\text{-}P^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of -$(L^1)_c$-P^1 and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0023] In another embodiment, the the therapeutic peptibody comprises a structure set out in Formula V

Formula V: $[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}P^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $-L^1\text{-}P^1\text{-}L^2\text{-}P^2$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0024] In another embodiment, the therapeutic peptibody is a multimer or dimer. In another embodiment, an aforementioned composition is provided wherein P^1, P^2, P^3 and/or P^4 are independently selected from a peptide set out in any one of Tables 4 through 38. In a related embodiment, P^1, P^2, P^3 and/or P^4 have the same amino acid sequence. In another embodiment, the Fc domain is set out in SEQ ID NO:1. In another embodiment, WSP is PEG. In still another embodiment, the Fc domain is et out in SEQ ID NO:1 and WSP is PEG. In another embodiment, the PEG has a molecular weight of between about 2 kDa and 100 kDa, or between 6 kDa and 25 kDa. In another embodiment, the composition comprises at least 50%, 75%, 85%, 90%, or 95% PEGylated therapeutic peptibody.

[0025] In yet another embodiment of the invention, an aforementioned composition is provided wherein the pH buffering agent is selected from the group consisting of glycine, histidine, glutamate, succinate, phosphate, acetate, and aspartate. In yet another embodiment of the invention, an aforementioned composition is provided wherein the bulking agent selected from the group consisting of mannitol, glycine, sucrose, dextran, polyvinylpyrolidone, carboxymethylcellulose, lactose, sorbitol, trehalose, or xylitol.

[0026] In yet another embodiment of the invention, an aforementioned composition is provided wherein the stabilizing agent selected from the group consisting of sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCL, poly-hydroxy compounds, including polysaccharides such as dextran, starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride.

[0027] In yet another embodiment of the invention, an aforementioned composition is provided wherein the surfactant selected from the group consisting of sodium lauryl sulfate, dioctyl sodium sulfosuccinate, dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, glycodeoxycholic acid sodium salt, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, hexadecyltrimethylammonium bromide, CHAPS, CHAPSO, SB3-10, SB3-12, digitonin,

Triton X-100, Triton X-114, lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 20, 40, 60, 65 and 80, soy lecithin, DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. In yet another embodiment of the invention, an aforementioned composition is provided wherein the therapeutic peptibody concentration is between about 0.25 mg/mL and 250 mg/mL.

[0028] In another embodiment of the invention, an aforementioned composition is provided wherein the pH buffering agent is 10 mM histidine and wherein the pH is 5.0; wherein the bulking agent is 4% w/v mannitol; wherein the stabilizing agent is 2% w/v sucrose; and wherein the surfactant is 0.004% w/v polysorbate-20. In another embodiment, the aforementioned composition is provided wherein P^1 comprises a sequence set forth in Table 6. In yet another embodiment of the invention, an aforementioned composition is provided wherein the therapeutic peptibody concentration is 0.5 mg/mL. In another embodiment, the therapeutic peptibody is any one of SEQ ID NO:993, SEQ ID NO:994, SEQ ID NO:995, SEQ ID NO:996, SEQ ID NO:997, SEQ ID NO:998, SEQ ID NO:999, SEQ ID NO:1000, SEQ ID NO:1001, SEQ ID NO:1002, SEQ ID NO:1003, SEQ ID NO:1004, SEQ ID NO:1005, SEQ ID NO:1006, SEQ ID NO:1007, SEQ ID NO:1008, SEQ ID NO:1009, SEQ ID NO:1010, SEQ ID NO:1011, SEQ ID NO:1012, SEQ ID NO:1013, SEQ ID NO:1014, SEQ ID NO:1015, SEQ ID NO:1016, or SEQ ID NO:1017.

[0029] In yet another embodiment of the invention, an aforementioned composition is provided wherein the pH buffering agent is 10 mM histidine and wherein the pH is 7.0; wherein the bulking agent is 4% w/v mannitol; wherein the stabilizing agent is 2% w/v sucrose; and wherein the surfactant is 0.01% w/v polysorbate-20. In another embodiment, the aforementioned composition is provided wherein P^1 comprises a sequence set forth in Table 32. In yet another embodiment of the invention, an aforementioned composition is provided wherein the therapeutic peptibody concentration is 30 mg/mL.

[0030] In still another embodiment of the invention, an aforementioned composition is provided wherein the pH buffering agent is 20 mM histidine and wherein the pH is 5.0; wherein the bulking agent is 3.3% w/v mannitol; wherein the stabilizing agent is 2% w/v sucrose; and wherein the surfactant is 0.01% w/v polysorbate-20. In another embodiment, the aforementioned composition is provided wherein P^1 comprises a sequence set forth in Table 4. In yet another embodiment of the invention, an aforementioned composition is provided wherein the therapeutic peptibody concentration is 100 mg/mL.

[0031] In still another embodiment of the invention, an aforementioned composition is provided wherein the pH buffering agent is 10 mM histidine and wherein the pH is 5.0; wherein the bulking agent is 2.5% w/v mannitol; and wherein the stabilizing agent is 3.5% w/v sucrose. In another embodiment, the aforementioned composition is provided wherein P^1 comprises a sequence set forth in Table 31. In yet another embodiment of the invention, an aforementioned composition is provided wherein the therapeutic peptibody concentration is 30 mg/mL.

[0032] In another embodiment of the invention, an aforementioned composition is provided wherein the composition is selected from the group consisting of: a) 10 mM histidine, pH 4.7, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20; b) 10 mM histidine, pH 5, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20; c) 10 mM glutamate, pH 4.5, 4% mannitol and 2% sucrose with and without 0.004% polysorbate-20; d) 10 mM succinate, pH 4.5, 4% mannitol and 2% sucrose, 0.004% polysorbate-20; e) 10 mM glutamate, pH 4.5, 9% sucrose, 0.004% polysorbate-20; f) 10 mM glutamate, pH 4.5, 4% mannitol, 2% sucrose, 1% hydroxyethyl starch, 0.004% polysorbate-20; g) 5 mM glutamate, pH 4.5, 2% mannitol, 1% sucrose, 0.004% polysorbate-20; and h) 10 mM glutamate, pH 4.5, 4% mannitol, 2% trehalose, 0.004% polysorbate-20. In another embodiment, the aforementioned composition is provided wherein P^1 comprises a sequence set forth in Tables 21-24. In still another embodiment, the aforementioned composition is provided wherein the therapeutic peptibody concentration is selected from the group consisting of 1, 30, 85, and 100 mg/mL.

[0033] The present invention also contemplates methods of making lyophilized therapeutic peptibodies of the present invention. In one embodiment, the invention provides a method for making a lyophilized therapeutic peptibody comprising the steps of: a) preparing a solution of a buffer, a bulking agent, a stabilizing agent, and a optionally surfactant; wherein the buffer is comprised of a pH buffering agent in a range of about 5 mM to about 20 mM and wherein the pH is in a range of about 3.0 to about 8.0; wherein the bulking agent is at a concentration of about 2.5% to about 4% w/v; wherein the stabilizing agent is at a concentration of about 0.1% to about 5% w/v; wherein the surfactant is at a concentration of about 0.004% to about 0.04% w/v; and b) lyophilizing the therapeutic peptibody; wherein the therapeutic peptibody comprises a structure set out in Formula I,

Formula I: $[(X^1)_a\text{-}F^1\text{-}(X^2)_b]\text{-}(L^1)_c\text{-}WSP_d$

wherein:

F^1 is an Fc domain;

X^1 is selected from

P^1-$(L^2)_e$-

P^2-$(L^3)_f$-P^1-$(L^2)_e$-

P^3-$(L^4)_g$-P^2-$(L^3)_f$-P^1-$(L^2)_e$- and

P^4-$(L^5)_h$-P^3-$(L^4)_g$-P^2-$(L^3)_f$-P^1-$(L^2)_e$-

X^2 is selected from:

-$(L^2)_e$-P^1,

-$(L^2)_e$-P^1-$(L^3)_f$-P^2,

-$(L^2)_e$-P^1-$(L^3)_f$-P^2-$(L^4)_g$-P^3, and

-$(L^2)_e$-P^1-$(L^3)_f$-P^2-$(L^4)_g$-P^3-$(L^5)_h$-P^4

wherein P^1, P^2, P^3, and P^4 are each independently sequences of pharmacologically active peptides;

L^1, L^2, L^3, L^4, and L^5 are each independently linkers;

a, b, c, e, f, g, and h are each independently 0 or 1,

provided that at least one of a and b is 1;

d is 0, 1, or greater than 1; and

WSP is a water soluble polymer, the attachment of which is effected at any reactive moiety in F^1.

[0034] In another embodiment, the aforementioned method is provided wherein thee therapeutic peptibody comprises a structure set out in Formula II

Formula II: $[X^1\text{-}F^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the C-terminus of X^1, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0035] In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody comprises a structure set out in Formula III

Formula III: $[F^1\text{-}X^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of X^2, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0036] In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody comprises a structure set out in Formula IV

Formula IV: $[F^1\text{-}(L^1)_e\text{-}P^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $\text{-}(L^1)_e\text{-}P^1$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0037] In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody comprises a structure set out in Formula V

Formula V: $[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}P^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $\text{-}L^1\text{-}P^1\text{-}L^2\text{-}P^2$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

[0038] In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody is a multimer or dimer. In another embodiment, the P^1, P^2, P^3 and/or P^4 are independently selected from a peptide set out in any one of Tables 4 through 38. In another embodiment, the P^1, P^2, P^3 and/or P^4 have the same amino acid sequence. In another embodiment, the Fc domain is set out in SEQ ID NO:1. In another embodiment, WSP is PEG. In another embodiment, the Fc domain is set out in SEQ ID NO:1 and WSP is PEG. In another embodiment, PEG has a molecular weight of between about 2 kDa and 100 kDa or between about 6 kDa and 25 kDa. In another embodiment, the aforementioned method is provided wherein the composition comprises at least 50%, 75%, 85%, 90%, or 95% PEGylated therapeutic peptibody.

[0039] In another embodiment, the aforementioned method is provided wherein the pH buffering agent is selected from the group consisting of glycine, histidine, glutamate, succinate, phosphate, acetate, and aspartate. In another embodiment, the aforementioned method is provided wherein the bulking agent selected from the group consisting of mannitol, glycine, sucrose, dextran, polyvinylpyrolidone, carboxymethylcellulose, lactose, sorbitol, trehalose, or xylitol. In another embodiment, the aforementioned method is provided wherein the stabilizing agent selected from the group consisting of sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCL, poly-hydroxy compounds, including polysaccharides such as dextran, starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride.

[0040] In another embodiment, the aforementioned method is provided wherein the surfactant selected from the group consisting of sodium lauryl sulfate, dioctyl sodium sulfosuccinate, dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate,

sodium deoxycholate, glycodeoxycholic acid sodium salt, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, hexadecyltrimethylammonium bromide, CHAPS, CHAPSO, SB3-10, SB3-12, digitonin, Triton X-100, Triton X-114, lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 20, 40, 60, 65 and 80, soy lecithin, DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody concentration is between about 0.25 mg/mL and 250 mg/mL.

[0041] In another embodiment, an aforementioned method is provided wherein the pH buffering agent is 10 mM histidine and wherein the pH is 5.0; wherein the bulking agent is 4% w/v mannitol; wherein the stabilizing agent is 2% w/v sucrose; and wherein the surfactant is 0.004% w/v polysorbate-20. In another embodiment, the aforementioned method is provided wherein P^1 comprises a sequence set forth in Table 6. In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody concentration is 0.5 mg/mL.

[0042] In another embodiment, an aforementioned method is provided wherein the pH buffering agent is 10 mM histidine and wherein the pH is 7.0; wherein the bulking agent is 4% w/v mannitol; wherein the stabilizing agent is 2% w/v sucrose; and wherein the surfactant is 0.01% w/v polysorbate-20. In another embodiment, the aforementioned method is provided wherein P^1 comprises a sequence set forth in Table 32. In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody concentration is 30 mg/mL.

[0043] In another embodiment, an aforementioned method is provided wherein the pH buffering agent is 20 mM histidine and wherein the pH is 5.0; wherein the bulking agent is 3.3% w/v mannitol; wherein the stabilizing agent is 2% w/v sucrose; and wherein the surfactant is 0.01% w/v polysorbate-20. In another embodiment, the aforementioned method is provided wherein P^1 comprises a sequence set forth in Table 4. In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody concentration is 100 mg/mL.

[0044] In another embodiment, an aforementioned method is provided wherein the pH buffering agent is 10 mM histidine and wherein the pH is 5.0; wherein the bulking agent is 2.5% w/v mannitol; and wherein the stabilizing agent is 3.5% w/v sucrose. In another embodiment, the aforementioned method is provided wherein P^1 comprises a sequence set

forth in Table 31. In another embodiment, the aforementioned method is provided wherein the therapeutic peptibody concentration is 30 mg/mL.

[0045] In another embodiment of the invention, an aforementioned method is provided wherein the composition is selected from the group consisting of: a) 10 mM histidine, pH 4.7, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20; b) 10 mM histidine, pH 5, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20; c) 10 mM glutamate, pH 4.5, 4% mannitol and 2% sucrose with and without 0.004% polysorbate-20; d) 10 mM succinate, pH 4.5, 4% mannitol and 2% sucrose, 0.004% polysorbate-20; e) 10 mM glutamate, pH 4.5, 9% sucrose, 0.004% polysorbate-20; f) 10 mM glutamate, pH 4.5, 4% mannitol, 2% sucrose, 1% hydroxyethyl starch, 0.004% polysorbate-20; g) 5 mM glutamate, pH 4.5, 2% mannitol, 1% sucrose, 0.004% polysorbate-20; and h) 10 mM glutamate, pH 4.5, 4% mannitol, 2% trehalose, 0.004% polysorbate-20. In another embodiment, the aforementioned method is provided wherein P^1 comprises a sequence set forth in Tables 21-24. In still another embodiment, the aforementioned method is provided wherein the therapeutic peptibody concentration is selected from the group consisting of 1, 30, 85, and 100 mg/mL.

[0046] In another embodiment, an aforementioned method is provided further comprising, prior to lyophilization, the steps of: b) adjusting the pH of the solution to a pH between about 4.0 and about 8.0; c) preparing a solution containing the therapeutic peptibody; d) buffer exchanging the solution of step (c) into the solution of step (b); e) adding an appropriate amount of a surfactant; and f) lyophilizing the mixture from step (e).

[0047] In another embodiment, the aforementioned method is provided wherein a method for preparing a reconstituted therapeutic peptibody composition is provided comprising the steps of: a) lyophilizing an aforementioned therapeutic peptibody composition; and b) reconstituting the lyophilized therapeutic peptibody composition.

[0048] In another embodiment, a kit for preparing an aqueous pharmaceutical composition is provided comprising a first container having an aforementioned lyophilized therapeutic peptibody composition, and a second container having a physiologically acceptable solvent for the lyophilized composition.

DETAILED DESCRIPTION OF THE INVENTION

Definition of terms

[0049] The term "comprising," with respect to a peptide compound, means that a compound may include additional amino acids on either or both of the amino or carboxy termini of the

given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound. With respect to a composition of the instant invention, the term "comprising" means that a composition may include additional components. These additional components should not significantly interfere with the activity of the composition.

[0050] The term "peptibody" refers to a molecule comprising peptide(s) fused either directly or indirectly to other molecules such as an Fc domain of an antibody, where the peptide moiety specifically binds to a desired target. The peptide(s) may be fused to either an Fc region or inserted into an Fc-Loop, a modified Fc molecule. Fc-Loops are described in U.S. Patent Application Publication No. US2006/0140934 incorporated herein by reference in its entirety. The invention includes such molecules comprising an Fc domain modified to comprise a peptide as an internal sequence (preferably in a loop region) of the Fc domain. 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 exemplified, insertions in any other non-terminal domains of the Fc are also considered part of this invention. The term "peptibody" does not include Fc-fusion proteins (e.g., full length proteins fused to an Fc domain).

[0051] The term "vehicle" refers to a molecule that prevents degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, or increases biological activity of a therapeutic protein. Exemplary vehicles include an Fc domain as described in U.S. Patent No. 5,428,130 to Capon et al., issued June 27, 1995.

[0052] The term "native Fc" refers to molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form. Typically, a native Fc comprises a CH2 and CH3 domain. The original immunoglobulin source of the native Fc is in one aspect of human origin and may be any of the immunoglobulins. A native Fc is a monomeric polypeptide that may be linked into dimeric or multimeric forms by covalent association (i.e., disulfide bonds), non-covalent association or a combination of both. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from one to four 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. Ellison et al. (1982), Nucleic Acids Res. 10: 4071-9. The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

[0053] 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. In one aspect, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. In another aspect, 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.

[0054] The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fcs, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means. In one embodiment, for example, the Fc region can be: DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K (SEQ ID NO:1).

[0055] Additional Fc sequences are known in the art and are contemplated for use in the invention. For example, Fc IgG1 (GenBank Accession No. P01857), Fc IgG2 (GenBank Accession No. P01859), Fc IgG3 (GenBank Accession No. P01860), Fc IgG4 (GenBank Accession No. P01861), Fc IgA1 (GenBank Accession No. P01876), Fc IgA2 (GenBank Accession No. P01877), Fc IgD (GenBank Accession No. P01880), Fc IgM (GenBank Accession No. P01871), and Fc IgE (GenBank Accession No. P01854) are some additional Fc sequences contemplated for use herein.

[0056] Optionally, an N-terminal amino acid sequence may be added to the above sequences (e.g., where expressed in bacteria).

[0057] 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.

[0058] The terms "derivatizing," "derivative" or "derivatized" mean processes and resulting compounds in which, for example and without limitation, (1) the compound has a cyclic portion; for example, cross-linking between cysteinyl residues within the compound; (2) the compound is cross-linked or has a cross-linking site; for example, the compound has a cysteinyl residue and thus forms cross-linked dimers in culture or in vivo; (3) one or more peptidyl linkage is replaced by a non-peptidyl linkage; (4) the N-terminus is replaced by -NRR$_1$, NRC(O)R$_1$, -NRC(O)OR$_1$, -NRS(O)$_2$R$_1$, -NHC(O)NHR, a succinimide group, or substituted or unsubstituted benzyloxycarbonyl-NH-, wherein R and R$_1$ and the ring substituents are as defined hereinafter; (5) the C-terminus is replaced by -C(O)R$_2$ or -NR$_3$R$_4$ wherein R$_2$, R$_3$ and R$_4$ are as defined hereinafter; and (6) compounds in which individual amino acid moieties are modified through treatment with agents capable of reacting with selected side chains or terminal residues. Derivatives are further described hereinafter.

[0059] As used herein the term "peptide" refers to molecules of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 ,14 ,15, 16 ,17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 ,39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more amino acids linked by peptide bonds. Peptides typically contain random and/or flexible conformations, such as random coils; and typically lack stable conformations, such as those observed in larger proteins/polypeptides, typically via secondary and tertiary structures. In particular embodiments, numerous size ranges of peptides are contemplated herein, such from about: 3-90, 3-80, 3-70, 3-60, 3-50; 5-90, 5-80, 5-70, 5-60, 5-50, 5-40, 5-30; 10-90, 10-80, 10-70, 10-60, 10-50, 10-40, 10-30; 10-20 amino acids in length, and the like. In further embodiments, the peptides used herein are no more than 100, 90, 80, 70, 60, 50, 40, 30, or 20 amino acids in length. Exemplary peptides may be generated by any of the methods set forth herein, such as carried in a peptide library (e.g., a phage display library), generated by chemical synthesis, derived by digestion of proteins, or generated using recombinant DNA techniques. Peptides include D and L form, either purified or in a mixture of the two forms.

[0060] Additionally, physiologically acceptable salts of the compounds of this invention are also contemplated. 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.

[0061] 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.

[0062] The term "pharmacologically active" means that a substance so described is determined to have activity that affects a medical parameter (e.g., but not limited to blood pressure, blood cell count, cholesterol level) or disease state (e.g., but not limited to cancer, autoimmune disorders). Thus, pharmacologically active peptides comprise agonistic or mimetic and antagonistic peptides as defined below.

[0063] The terms "-mimetic peptide" and "-agonist peptide" refer to a peptide having biological activity comparable to a protein (e.g., but not limited to EPO, TPO, G-CSF and other proteins described herein) 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 Tables 2 and 7. As an example, 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.

[0064] As another example, the term "TPO-mimetic peptide" or "TMP" refers to 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 and any other reference in Table 2 identified as having TPO-mimetic subject matter, as well as International application WO 00/24770 published May 4, 2000, 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.

[0065] As another example, the term "G-CSF-mimetic peptide" refers to any peptides that can be identified or described in Paukovits et al. (1984), Hoppe-Seylers Z. Physiol. Chem. 365: 303-11 or any of the references in Table 2 identified as having G-CSF-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.

[0066] The term "CTLA4-mimetic peptide" refers to any peptides that can be identified or derived as described in Fukumoto et al. (1998), Nature Biotech. 16: 267-70. 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.

[0067] 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.

[0068] The terms "IL-1 antagonist" and "IL-1ra-mimetic peptide" refers to peptides that inhibit or down-regulate activation of the IL-1 receptor by IL-1. IL-1 receptor activation results from formation of a complex among IL-1, IL-1 receptor, and IL-1 receptor accessory protein. IL-1 antagonist or IL-1ra-mimetic peptides bind to IL-1, IL-1 receptor, or IL-1 receptor accessory protein and obstruct complex formation among any two or three components of the complex. Exemplary IL-1 antagonist or IL-1ra-mimetic peptides can be identified or derived as described in U.S. Pat. Nos. 5,608,035; 5,786,331, 5,880,096; or any of the references in Table 2 identified as having IL-1ra-mimetic or IL-1 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.

[0069] The term "VEGF-antagonist peptide" refers to peptides that can be identified or derived as described in Fairbrother (1998), Biochem. 37: 17754-64, and in any of the references in Table 2 identified as having VEGF-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.

[0070] The term "MMP inhibitor peptide" refers to peptides that can be identified or derived as described in Koivunen (1999), Nature Biotech. 17: 768-74 and in any of the references in Table 2 identified as having MMP inhibitory 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.

[0071] The term "myostatin inhibitor peptide" refers to peptides that can be identified by their ability to reduce or block myostatin activity or signaling as demonstrated in *in vitro* assays such as, for example the pMARE C2C12 cell-based myostatin activity assay or by *in vivo* animal testing as described in U.S. patent application Publication No US20040181033A1 and PCT application publication No. WO2004/058988. Exemplary myostatin inhibitor peptides are set out in Tables 21-24.

[0072] The term "integrin/adhesion antagonist" refers to peptides that inhibit or down-regulate the activity of integrins, selectins, cell adhesion molecules, integrin receptors, selectin receptors, or cell adhesion molecule receptors. Exemplary integrin/adhesion antagonists comprise laminin, echistatin, the peptides described in Tables 25-28.

[0073] The term "bone resorption inhibitor" refers to such molecules as determined by the assays of Examples 4 and 11 of WO 97/23614:, which is hereby incorporated by reference in its entirety. Exemplary bone resorption inhibitors include OPG and OPG-L antibody, which are described in WO 97/23614 and WO98/46751, respectively, which are hereby incorporated by reference in their entirety.

[0074] The term "nerve growth factor inhibitor" or "nerve growth factor agonist" refers to a peptide that binds to and inhibits nerve growth factor (NGF) activity or signaling. Exemplary peptides of this type are set out in Table 29.

[0075] The term "TALL-1 modulating domain" refers to any amino acid sequence that binds to the TALL-1 and comprises naturally occurring sequences or randomized sequences. Exemplary TALL-1 modulating domains can be identified or derived by phage display or other methods mentioned herein. Exemplary peptides of this type are set out in Tables 30 and 31.

[0076] The term " TALL-1 antagonist" refers to a molecule that binds to the TALL-1 and increases or decreases one or more assay parameters opposite from the effect on those parameters by full length native TALL-1. Such activity can be determined, for example, by

such assays as described in the subsection entitled "Biological activity of AGP-3" in the Materials & Methods section of the patent application entitled, "TNF-RELATED PROTEINS", WO 00/47740, published August 17, 2000.

[0077] The term "Ang 2-antagonist peptide" refers to peptides that can be identified or derived as having Ang-2-antagonistic characteristics. Exemplary peptides of this type are set out in Tables 32-38 .

[0078] The term "WSP" refers to a water soluble polymer which prevents a peptide, protein or other compound to which it is attached from precipitating in an aqueous environment, such as, by way of example, a physiological environment. A more detailed description of various WSP embodiments contemplated by the invention follows.

Lyophilization and Administration

[0079] Therapeutic peptibodies are useful in pharmaceutical formulations in order to treat human diseases as described herein. In one embodiment the therapeutic peptibody compositions are lyophilized. Lyophilization is carried out using techniques common in the art and should be optimized for the composition being developed [Tang et al., Pharm Res. 21:191-200, (2004) and Chang et al., Pharm Res. 13:243-9 (1996)].

[0080] A lyophilization cycle is, in one aspect, composed of three steps: freezing, primary drying, and secondary drying [A.P. Mackenzie, Phil Trans R Soc London, Ser B, Biol 278:167 (1977)]. In the freezing step, the solution is cooled to initiate ice formation. Furthermore, this step induces the crystallization of the bulking agent. The ice sublimes in the primary drying stage, which is conducted by reducing chamber pressure below the vapor pressure of the ice, using a vacuum and introducing heat to promote sublimation. Finally, adsorbed or bound water is removed at the secondary drying stage under reduced chamber pressure and at an elevated shelf temperature. The process produces a material known as a lyophilized cake. Thereafter the cake can be reconstituted with either sterile water or suitable diluent for injection.

[0081] The lyophilization cycle not only determines the final physical state of the excipients but also affects other parameters such as reconstitution time, appearance, stability and final moisture content. The composition structure in the frozen state proceeds through several transitions (e.g., glass transitions, wettings, and crystallizations) that occur at specific temperatures and can be used to understand and optimize the lyophilization process. The glass transition temperature (Tg and/or Tg') can provide information about the physical state of a solute and can be determined by differential scanning calorimetry (DSC). Tg and Tg'

are an important parameter that must be taken into account when designing the lyophilization cycle. For example, Tg' is important for primary drying. Furthermore, in the dried state, the glass transition temperature provides information on the storage temperature of the final product.

[0082] Excipients in general

[0083] Excipients are additives that are included in a formulation because they either impart or enhance the stability, delivery and manufacturability of a drug product. Regardless of the reason for their inclusion, excipients are an integral component of a drug product and therefore need to be safe and well tolerated by patients. For protein drugs, the choice of excipients is particularly important because they can affect both efficacy and immunogenicity of the drug. Hence, protein formulations need to be developed with appropriate selection of excipients that afford suitable stability, safety, and marketability.

[0084] A lyophilized formulation is usually comprised of a buffer, a bulking agent, and a stabilizer. The utility of a surfactant may be evaluated and selected in cases where aggregation during the lyophilization step or during reconstitution becomes an issue. An appropriate buffering agent is included to maintain the formulation within stable zones of pH during lyophilization. A comparison of the excipient components in liquid and lyophilized protein formulations is provided in Table A.

Table A: Excipient components of lyophilized protein formulations

Excipient component	Function in lyophilized formulation
Buffer	o Maintain pH of formulation during lyophilization and upon reconstitution
Tonicity agent/ stabilizer	o Stabilizers include cryo and lyoprotectants o Examples include Polyols, sugars and polymers o Cryoprotectants protect proteins from freezing stresses o Lyoprotectants stabilize proteins in the freeze-dried state
Bulking agent	o Used to enhance product elegance and to prevent blowout o Provides structural strength to the lyo cake o Examples include mannitol and glycine

Surfactant	o Employed if aggregation during the lyophilization process is an issue o May serve to reduce reconstitution times o Examples include polysorbate 20 and 80
Anti-oxidant	o Usually not employed, molecular reactions in the lyo cake are greatly retarded
Metal ions/chelating agent	o May be included if a specific metal ion is included only as a co-factor or where the metal is required for protease activity o Chelating agents are generally not needed in lyo formulations
Preservative	o For multi-dose formulations only o Provides protection against microbial growth in formulation o Is usually included in the reconstitution diluent (e.g. bWFI)

[0085] The principal challenge in developing formulations for therapeutic proteins is stabilizing the product against the stresses of manufacturing, shipping and storage. The role of formulation excipients is to provide stabilization against these stresses. Excipients may also be employed to reduce viscosity of high concentration protein formulations in order to enable their delivery and enhance patient convenience. In general, excipients can be classified on the basis of the mechanisms by which they stabilize proteins against various chemical and physical stresses. Some excipients are used to alleviate the effects of a specific stress or to regulate a particular susceptibility of a specific protein. Other excipients have more general effects on the physical and covalent stabilities of proteins. The excipients described herein are organized either by their chemical type or their functional role in formulations. Brief descriptions of the modes of stabilization are provided when discussing each excipient type.

[0086] Given the teachings and guidance provided herein, those skilled in the art will know what amount or range of excipient can be included in any particular formulation to achieve a

biopharmaceutical formulation of the invention that promotes retention in stability of the biopharmaceutical. For example, the amount and type of a salt to be included in a biopharmaceutical formulation of the invention can be selected based on to the desired osmolality (i.e., isotonic, hypotonic or hypertonic) of the final solution as well as the amounts and osmolality of other components to be included in the formulation. Similarly, by exemplification with reference to the type of polyol or sugar included in a formulation, the amount of such an excipient will depend on its osmolality.

[0087] By way of example, inclusion of about 5% sorbitol can achieve isotonicity while about 9% of a sucrose excipient is needed to achieve isotonicity. Selection of the amount or range of concentrations of one or more excipients that can be included within a biopharmaceutical formulation of the invention has been exemplified above by reference to salts, polyols and sugars. However, those skilled in the art will understand that the considerations described herein and further exemplified by reference to specific excipients are equally applicable to all types and combinations of excipients including, for example, salts, amino acids, other tonicity agents, surfactants, stabilizers, bulking agents, cryoprotectants, lyoprotectants, anti-oxidants, metal ions, chelating agents and/or preservatives.

[0088] Further, where a particular excipient is reported in a formulation by, e.g., percent (%) w/v, those skilled in the art will recognize that the equivalent molar concentration of that excipient is also contemplated.

[0089] Of course, a person having ordinary skill in the art would recognize that the concentrations of the aforementioned excipients share an interdependency within a particular formulation. By way of example, the concentration of a bulking agent may be lowered where, e.g., there is a high protein/peptide concentration or where, e.g., there is a high stabilizing agent concentration. In addition, a person having ordinary skill in the art would recognize that, in order to maintain the isotonicity of a particular formulation in which there is no bulking agent, the concentration of a stabilizing agent would be adjusted accordingly (i.e., a "tonicifying" amount of stabilizer would be used). Other excipients are known in the art and can be found in Powell et al., Compendium of Excipients fir Parenteral Formulations (1998), PDA J. Pharm. Sci. Technology, 52:238-311.

[0090] Buffers

[0091] The stability of a protein drug is usually observed to be maximal in a narrow pH range. This pH range of optimal stability needs to be identified early during pre-formulation studies. Several approaches such as accelerated stability studies and calorimetric screening

studies have been demonstrated to be useful in this endeavor (Remmele R.L. Jr., et al., *Biochemistry*, 38(16): 5241-7 (1999)). Once a formulation is finalized, the drug product must be manufactured and maintained within a predefined specification throughout its shelf-life. Hence, buffering agents are almost always employed to control pH in the formulation.

[0092] Organic acids, phosphates and Tris have been employed routinely as buffers in protein formulations (Table B). The buffer capacity of the buffering species is maximal at a pH equal to the pKa and decreases as pH increases or decreases away from this value. Ninety percent of the buffering capacity exists within one pH unit of its pKa. Buffer capacity also increases proportionally with increasing buffer concentration.

[0093] Several factors need to be considered when choosing a buffer. First and foremost, the buffer species and its concentration need to be defined based on its pKa and the desired formulation pH. Equally important is to ensure that the buffer is compatible with the protein drug, other formulation excipients, and does not catalyze any degradation reactions. Recently, polyanionic carboxylate buffers such as citrate and succinate have been shown to form covalent adducts with the side chain residues of proteins. A third important aspect to be considered is the sensation of stinging and irritation the buffer may induce. For example, citrate is known to cause stinging upon injection (Laursen T, et al., *Basic Clin Pharmacol Toxicol.*, 98(2): 218-21 (2006)). The potential for stinging and irritation is greater for drugs that are administered via the SC or IM routes, where the drug solution remains at the site for a relatively longer period of time than when administered by the IV route where the formulation gets diluted rapidly into the blood upon administration. For formulations that are administered by direct IV infusion, the total amount of buffer (and any other formulation component) needs to be monitored. One has to be particularly careful about potassium ions administered in the form of the potassium phosphate buffer, which can induce cardiovascular effects in a patient (Hollander-Rodriguez JC, et al., *Am. Fam. Physician.*, 73(2): 283-90 (2006)).

[0094] Buffers for lyophilized formulations need additional consideration. Some buffers like sodium phosphate can crystallize out of the protein amorphous phase during freezing resulting in rather large shifts in pH. Other common buffers such as acetate and imidazole should be avoided since they may sublime or evaporate during the lyophilization process, thereby shifting the pH of formulation during lyophilization or after reconstitution.

Table B: Commonly used buffering agents and their pK_a values

Buffer	pK_a	Example drug product
Acetate	4.8	Neupogen, Neulasta
Succinate	pK_{a1} = 4.8, pK_{a2} = 5.5	Actimmune
Citrate	pK_{a1} = 3.1, pK_{a2} = 4.8, pK_{a3} = 6.4	Humira
Histidine (imidazole)	6.0	Xolair
phosphate	pK_{a1} = 2.15, pK_{a2} = 7.2, pK_{a3} = 12.3	Enbrel (liquid formulation)
Tris	8.1	Leukine

[0095] The buffer system present in the compositions is selected to be physiologically compatible and to maintain a desired pH in the reconstituted solution as well as in the solution before lyophilization. In one embodiment, the pH of the solution prior to lyophilization is between pH 2.0 and pH 12.0. For example, in one embodiment the pH of the solution prior to lyophilization is 2.0, 2.3., 2.5.,2.7, 3.0, 3.3, 3.5, 3.7, 4.0, 4.3, 4.5, 4.7, 5.0, 5.3, 5.5, 5.7, 6.0, 6.3, 6.5, 6.7, 7.0, 7.3, 7.5, 7.7, 8.0, 8.3, 8.5, 8.7, 9.0, 9.3,9.5,9.7, 10.0, 10.3, 10.5, 10.7, 11.0, 11.3, 11.5, 11.7, or 12.0. In another embodiment, the pH of the reconstituted solution is between 4.5 and 9.0. In one embodiment, the pH in the reconstituted solution is 4.5, 4.7, 5.0, 5.3, 5.5, 5.7, 6.0, 6.3, 6.5, 6.7, 7.0, 7.3, 7.5, 7.7, 8.0, 8.3, 8.5, 8.7, or 9.0.

[0096] In one embodiment, the pH buffering agent used in the formulation is an amino acid or mixture of amino acids. In one aspect, the pH buffering agent is histidine or a mixture of amino acids one of which is histidine.

[0097] The pH buffering compound may be present in any amount suitable to maintain the pH of the formulation at a predetermined level. In one embodiment, when the pH buffering agent is an amino acid, the concentration of the amino acid is between 0.1 mM and 1000 mM (1 M). In one embodiment, the pH buffering agent is at least 0.1, 0.5, 0.7, 0.8 0.9, 1.0, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, 700, or 900 mM. In another embodiment, the concentration of the pH buffering agent is between 1, 1.2, 1.5, 1.7, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50, 60, 70, 80, or 90 mM and 100 mM. In still another embodiment, the concentration of the pH buffering agent is between 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,

18, 19, 20, 30, or 40 mM and 50 mM. In yet another embodiment, the concentration of the pH buffering agent is 10 mM.

[0098] Other exemplary pH buffering agents used to buffer the formulation as set out herein include, but are not limited to glycine, histidine, glutamate, succinate, phosphate, acetate, and aspartate.

[0099] Stabilizers and bulking agents

[00100] Bulking agents are typically used in lyophilized formulations to enhance product elegance and to prevent blowout. Conditions in the formulation are generally designed so that the bulking agent crystallizes out of the frozen amorphous phase (either during freezing or annealing above the Tg') giving the cake structure and bulk. Mannitol and glycine are examples of commonly used bulking agents.

[00101] Stabilizers include a class of compounds that can serve as cryoprotectants, lyoprotectants, and glass forming agents. Cryoprotectants act to stabilize proteins during freezing or in the frozen state at low temperatures (P. Cameron, ed., Good Pharmaceutical Freeze-Drying Practice, Interpharm Press, Inc., Buffalo Grove, IL, (1997)). Lyoprotectants stabilize proteins in the freeze-dried solid dosage form by preserving the native-like conformational properties of the protein during dehydration stages of freeze-drying. Glassy state properties have been classified as "strong" or "fragile" depending on their relaxation properties as a function of temperature. It is important that cryoprotectants, lyoprotectants, and glass forming agents remain in the same phase with the protein in order to impart stability. Sugars, polymers, and polyols fall into this category and can sometimes serve all three roles.

[00102] Polyols encompass a class of excipients that includes sugars, (e.g. mannitol, sucrose, sorbitol), and other polyhydric alcohols (e.g., glycerol and propylene glycol). The polymer polyethylene glycol (PEG) is included in this category. Polyols are commonly used as stabilizing excipients and/or isotonicity agents in both liquid and lyophilized parenteral protein formulations. With respect to the Hofmeister series, the polyols are kosmotropic and are preferentially excluded from the protein surface. Polyols can protect proteins from both physical and chemical degradation pathways. Preferentially excluded co-solvents increase the effective surface tension of solvent at the protein interface whereby the most energetically favorable protein conformations are those with the smallest surface areas.

[00103] Mannitol is a popular bulking agent in lyophilized formulations because it crystallizes out of the amorphous protein phase during freeze-drying lending structural stability to the cake (e.g. Leukine ®, Enbrel ® – Lyo, Betaseron®). It is generally used in

combination with a cryo and/or lyoprotectant like sucrose. Because of the propensity of mannitol to crystallize under frozen conditions, sorbitol and sucrose are the preferred tonicity agents/stabilizers in liquid formulations to protect the product against freeze-thaw stresses encountered during transport or when freezing bulk prior to manufacturing. Sorbitol and sucrose are far more resistant to crystallization and therefore less likely to phase separate from the protein. It is interesting to note that while mannitol has been used in tonicifying amounts in several marketed liquid formulations such as Actimmune®, Forteo®, and Rebif®, the product labels of these drugs carry a 'Do Not Freeze' warning. The use of reducing sugars (containing free aldehyde or ketone groups) such as glucose and lactose should be avoided because they can react and glycate surface lysine and arginine residues of proteins via the Maillard reaction of aldehydes and primary amines (Chevalier F, et al., *Nahrung*, 46(2): 58-63 (2002); Humeny A, et al., *J Agric Food Chem.* 50(7): 2153-60 (2002)). Sucrose can hydrolyze to fructose and glucose under acidic conditions (Kautz C. F. and Robinson A. L., *JACS*, 50(4) 1022-30 (1928)), and consequently may cause glycation.

[00104] The polymer polyethylene glycol (PEG) could stabilize proteins by two different temperature dependent mechanisms. At lower temperatures, it is preferentially excluded from the protein surface but has been shown to interact with the unfolded form of the protein at higher temperature given its amphipathic nature (Lee L.L., and Lee J.C., *Biochemistry*, 26(24): 7813-9 (1987)). Thus at lower temperatures it may protect proteins via the mechanism of preferential exclusion, but at higher temperatures possibly by reducing the number of productive collisions between unfolded molecules. PEG is also a cryoprotectant and has been employed in Recombinate®, a lyophilized formulation of recombinant Antihemophilic Factor, which utilizes PEG 3350 at a concentration of 1.5 mg/mL. The low molecular weight liquid PEGs (PEG 300 – 600) can be contaminated with peroxides and cause protein oxidation. If used, the peroxide content in the raw material must be minimized and controlled throughout its shelf-life. The same holds true for polysorbates.

[00105] In a particular embodiment of the present compositions, a stabilizer (or a combination of stabilizers) is added to the lyophilization formulation to prevent or reduce lyophilization-induced or storage-induced aggregation and chemical degradation. A hazy or turbid solution upon reconstitution indicates that the protein has precipitated. The term "stabilizer" means an excipient capable of preventing aggregation or other physical degradation, as well as chemical degradation (for example, autolysis, deamidation, oxidation, etc.) in an aqueous and solid state. Stabilizers that are conventionally employed in pharmaceutical compositions include, but are not limited to, sucrose, trehalose, mannose,

maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCL, poly-hydroxy compounds, including polysaccharides such as dextran, starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride, [Carpenter et al., Develop. Biol. Standard 74:225, (1991)]. In one embodiment, the stabilizer is incorporated in a concentration of about 0% to about 40% w/v. In another embodiment, the stabilizer is incorporated in a concentration of at least 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, or 40% w/v. In another embodiment, the stabilizer is incorporated in a concentration of about 1, 2, 3, 4, 5, 6, 7, 8, 9% to about 10% w/v. In still another embodiment, the stabilizer is incorporated in a concentration of about 2% to about 4% w/v. In yet another embodiment, the stabilizer is incorporated in a concentration of about 2% w/v.

[00106] If desired, the lyophilized compositions also include appropriate amounts of bulking and osmolarity regulating agents suitable for forming a lyophilized "cake". Bulking agents may be either crystalline (for example, mannitol, glycine) or amorphous (for example, sucrose, polymers such as dextran, polyvinylpyrolidone, carboxymethylcellulose). Other exemplary bulking agents include lactose, sorbitol, trehalose, or xylitol. In one embodiment, the bulking agent is mannitol. In a further embodiment, the bulking agent is incorporated in a concentration of about 0% to about 10% w/v. In another embodiment, the bulking agent is incorporated in a concentration of at least 0.2, 0.5, 0.7, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, or 9.5% w/v. In a yet further embodiment in a concentration of about 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5% to 5.0% w/v, to produce a mechanically and pharmaceutically stable and elegant cake. In another embodiment, the mannitol concentration is 4% w/v.

[00107] Surfactants

[00108] Protein molecules have a high propensity to interact with surfaces making them susceptible to adsorption and denaturation at air-liquid, vial-liquid, and liquid-liquid (silicone oil) interfaces. This degradation pathway has been observed to be inversely dependent on protein concentration and result in either the formation of soluble and insoluble protein aggregates or the loss of protein from solution via adsorption to surfaces. In addition to container surface adsorption, surface-induced degradation is exacerbated with physical agitation, as would be experienced during shipping and handling of the product.

[00109] Surfactants are commonly used in protein formulations to prevent surface-induced degradation. Surfactants are amphipathic molecules with the capability of out-competing proteins for interfacial positions. Hydrophobic portions of the surfactant

molecules occupy interfacial positions (e.g., air/liquid), while hydrophilic portions of the molecules remain oriented towards the bulk solvent. At sufficient concentrations (typically around the detergent's critical micellar concentration), a surface layer of surfactant molecules serve to prevent protein molecules from adsorbing at the interface. Thereby, surface-induced degradation is minimized. The most commonly used surfactants are fatty acid esters of sorbitan polyethoxylates, i.e. polysorbate 20 and polysorbate 80 (e.g., Avonex®, Neupogen®, Neulasta®). The two differ only in the length of the aliphatic chain that imparts hydrophobic character to the molecules, C-12 and C-18, respectively. Accordingly, polysorbate-80 is more surface-active and has a lower critical micellar concentration than polysorbate-20. The surfactant poloxamer 188 has also been used in several marketed liquid products such Gonal-F ®, Norditropin ®, and Ovidrel ®.

[00110] Detergents can also affect the thermodynamic conformational stability of proteins. Here again, the effects of a given excipient will be protein specific. For example, polysorbates have been shown to reduce the stability of some proteins and increase the stability of others. Detergent destabilization of proteins can be rationalized in terms of the hydrophobic tails of the detergent molecules that can engage in specific binding with partially or wholly unfolded protein states. These types of interactions could cause a shift in the conformational equilibrium towards the more expanded protein states (i.e. increasing the exposure of hydrophobic portions of the protein molecule in complement to binding polysorbate). Alternatively, if the protein native state exhibits some hydrophobic surfaces, detergent binding to the native state may stabilize that conformation.

[00111] Another aspect of polysorbates is that they are inherently susceptible to oxidative degradation. Often, as raw materials, they contain sufficient quantities of peroxides to cause oxidation of protein residue side-chains, especially methionine. The potential for oxidative damage arising from the addition of stabilizer emphasizes the point that the lowest effective concentrations of excipients should be used in formulations. For surfactants, the effective concentration for a given protein will depend on the mechanism of stabilization. It has been postulated that if the mechanism of surfactant stabilization is related to preventing surface-denaturation the effective concentration will be around the detergent's critical micellar concentration. Conversely, if the mechanism of stabilization is associated with specific protein-detergent interactions, the effective surfactant concentration will be related to the protein concentration and the stoichiometry of the interaction (Randolph T.W., et al., *Pharm Biotechnol.*, 13:159-75 (2002)).

[00112] Surfactants may also be added in appropriate amounts to prevent surface related aggregation phenomenon during freezing and drying [Chang, B, J. Pharm. Sci. 85:1325, (1996)]. Exemplary surfactants include anionic, cationic, nonionic, zwitterionic, and amphoteric surfactants including surfactants derived from naturally-occurring amino acids. Anionic surfactants include, but are not limited to, sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, and glycodeoxycholic acid sodium salt. Cationic surfactants include, but are not limited to, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, and hexadecyltrimethylammonium bromide. Zwitterionic surfactants include, but are not limited to, CHAPS, CHAPSO, SB3-10, and SB3-12. Non-ionic surfactants include, but are not limited to, digitonin, Triton X-100, Triton X-114, TWEEN-20, and TWEEN-80. In another embodiment, surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, soy lecithin and other phospholipids such as DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. Compositions comprising these surfactants, either individually or as a mixture in different ratios, are therefore further provided. In one embodiment, the surfactant is incorporated in a concentration of about 0% to about 5% w/v. In another embodiment, the surfactant is incorporated in a concentration of at least 0.001, 0.002, 0.005, 0.007, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, or 4.5% w/v. In another embodiment, the surfactant is incorporated in a concentration of about 0.001% to about 0.5% w/v. In still another embodiment, the surfactant is incorporated in a concentration of about 0.004, 0.005, 0.007, 0.01, 0.05, or 0.1% w/v to about 0.2% w/v. In yet another embodiment, the surfactant is incorporated in a concentration of about 0.01% to about 0.1% w/v.

[00113] Salts

[00114] Salts are often added to increase the ionic strength of the formulation, which can be important for protein solubility, physical stability, and isotonicity. Salts can affect the physical stability of proteins in a variety of ways. Ions can stabilize the native state of proteins by binding to charged residues on the protein's surface. Alternatively, they can stabilize the denatured state by binding to the peptide groups along the protein backbone (-CONH-). Salts can also stabilize the protein native conformation by shielding repulsive electrostatic interactions between residues within a protein molecule. Electrolytes in protein

formulations can also shield attractive electrostatic interactions between protein molecules that can lead to protein aggregation and insolubility.

[00115] The effect of salt on the stability and solubility of proteins varies significantly with the characteristics of the ionic species. The Hofmeister series originated in the 1880's as a way to rank order electrolytes based on their ability to precipitate proteins (Cacace M.G., et al., *Quarterly Reviews of Biophysics.*, 30(3): 241-277 (1997)). In this report, the Hofmeister series is used to illustrate a scale of protein stabilization effects by ionic and non-ionic co-solutes. In Table C, co-solutes are ordered with respect to their general effects on solution state proteins, from stabilizing (kosmotropic) to destabilizing (chaotropic). In general, the differences in effects across the anions are far greater than that observed for the cations, and, for both types, the effects are most apparent at higher concentrations than are acceptable in parenteral formulations. High concentrations of kosmotropes (e.g., >1 molar ammonium sulfate) are commonly used to precipitate proteins from solution by a process called 'salting-out' where the kosmotrope is preferentially excluded from the protein surface reducing the solubility of the protein in it's native (folded) conformation. Removal or dilution of the salt will return the protein to solution. The term 'salting-in' refers to the use of destabilizing ions (e.g., like guanidine and chloride) that increase the solubility of proteins by solvating the peptide bonds of the protein backbone. Increasing concentrations of the chaotrope will favor the denatured (unfolded) state conformation of the protein as the solubility of the peptide chain increases. The relative effectiveness of ions to 'salt-in' and 'salt-out' defines their position in the Hofmeister series.

[00116] In order to maintain isotonicity in a parenteral formulation, salt concentrations are generally limited to less than 150 mM for monovalent ion combinations. In this concentration range, the mechanism of salt stabilization is probably due to screening of electrostatic repulsive intramolecular forces or attractive intermolecular forces (Debye-Huckel screening). Interestingly, chaotropic salts have been shown to be more effective at stabilizing the protein structure than similar concentrations of kosmotropes by this mechanism. The chaotropic anions are believed to bind more strongly than the kosmotropic ions. With respect to covalent protein degradation, differential effects of ionic strength on this mechanism are expected through Debye-Huckel theory. Accordingly, published reports of protein stabilization by sodium chloride are accompanied by those where sodium chloride accelerated covalent degradation. The mechanisms by which salts affect protein stability are protein specific and may vary significantly as a function of solution pH. An example where an excipient can be useful in enabling the delivery of a protein drug is that of some high

concentration antibody formulations. Recently, salts have been shown to be effective in reducing the viscosity of such formulations (Liu J., et al., *J. Pharm Sci.*, 94(9): 1928-40 (2005); Erratum in: *J Pharm Sci.*, 95(1): 234-5. (2006)).

Table C: The Hofmeister series of salts

Cosolute			Stabilization scales	
Anion	Cation	Other		
F^-	$(CH_3)_4N^+$	Glycerol/Sorbitol	Stabilizing	*Kosmotropic*
PO_4^-	$(CH_3)_2NH^+$	Sucrose/Trehalose	*(salting-out)*	
SO_4^-	NH_4^+	TMAO	⇕	⇕
$CHCOO^-$	K^+			
Cl^-	Na^+			
Br^-	Cs^+			
I^-	Li^+			
	Mg^{2+}	Guanidine		
	Ca^{2+}	Arginine		
	Ba^{2+}	Urea	*Destabilizing* *(salting-in)*	*Chaotropic*

[00117] Amino acids

[00118] Amino acids have found versatile use in protein formulations as buffers, bulking agents, stabilizers and antioxidants. Histidine and glutamic acid are employed to buffer protein formulations in the pH range of 5.5 – 6.5 and 4.0 – 5.5 respectively. The imidazole group of histidine has a pKa = 6.0 and the carboxyl group of glutamic acid side chain has a pKa of 4.3 which makes them suitable for buffering in their respective pH ranges. Acetate, the most commonly used buffer in the acidic pH range of 4.0 – 5.5, sublimates during lyophilization and hence should not be used in freeze-dried formulations. Glutamic acid is particularly useful in such cases (e.g., Stemgen®). Histidine is commonly found in marketed protein formulations (e.g., Xolair®, Herceptin®, Recombinate®). It provides a good alternative to citrate, a buffer known to sting upon injection. Interestingly, histidine has also been reported to have a stabilizing effect on ABX-IL8 (an IgG2 antibody) with respect to

aggregation when used at high concentrations in both liquid and lyophilized presentations (Chen B, et al., *Pharm Res.*, 20(12): 1952-60 (2003)). Histidine (up to 60 mM) was also observed to reduce the viscosity of a high concentration formulation of this antibody. However, in the same study, the authors observed increased aggregation and discoloration in histidine containing formulations during freeze-thaw studies of the antibody in stainless steel containers. The authors attributed this to an effect of iron ions leached from corrosion of steel containers. Another note of caution with histidine is that it undergoes photo-oxidation in the presence of metal ions (Tomita M, et al., *Biochemistry*, 8(12): 5149-60 (1969)). The use of methionine as an antioxidant in formulations appears promising; it has been observed to be effective against a number of oxidative stresses (Lam XM, et al., *J Pharm Sci.*, 86(11): 1250-5 (1997)).

[00119] The amino acids glycine, proline, serine and alanine have been shown to stabilize proteins by the mechanism of preferential exclusion. Glycine is also a commonly used bulking agent in lyophilized formulations (e.g., Neumega ®, Genotropin®, Humatrope®). It crystallizes out of the frozen amorphous phase giving the cake structure and bulk. Arginine has been shown to be an effective agent in inhibiting aggregation and has been used in both liquid and lyophilized formulations (e.g., Activase®, Avonex®, Enbrel® liquid). Furthermore, the enhanced efficiency of refolding of certain proteins in the presence of arginine has been attributed to its suppression of the competing aggregation reaction during refolding.

[00120] Antioxidants

[00121] Oxidation of protein residues arises from a number of different sources. Beyond the addition of specific antioxidants, the prevention of oxidative protein damage involves the careful control of a number of factors throughout the manufacturing process and storage of the product such as atmospheric oxygen, temperature, light exposure, and chemical contamination. The most commonly used pharmaceutical antioxidants are reducing agents, oxygen/free-radical scavengers, or chelating agents. Antioxidants in therapeutic protein formulations must be water-soluble and remain active throughout the product shelf-life. Reducing agents and oxygen/free-radical scavengers work by ablating active oxygen species in solution. Chelating agents such as EDTA can be effective by binding trace metal contaminants that promote free-radical formation. For example, EDTA was utilized in the liquid formulation of acidic fibroblast growth factor to inhibit the metal ion catalyzed oxidation of cysteine residues. EDTA has been used in marketed products like Kineret® and Ontak®.

[00122] In addition to evaluating the effectiveness of various excipients at preventing protein oxidation, formulation scientists must be aware of the potential for the antioxidants themselves to induce other covalent or physical changes to the protein. A number of such cases have been reported in the literature. Reducing agents (like glutathione) can cause disruption of intramolecular disulfide linkages, which can lead to disulfide shuffling. In the presence of transition metal ions, ascorbic acid and EDTA have been shown to promote methionine oxidation in a number of proteins and peptides (Akers MJ, and Defelippis MR. Peptides and Proteins as Parenteral Solutions. In: Pharmaceutical Formulation Development of Peptides and Proteins. Sven Frokjaer, Lars Hovgaard, editors. Pharmaceutical Science. Taylor and Francis, UK (1999)); Fransson J.R., *J. Pharm. Sci.* 86(9): 4046-1050 (1997); Yin J, et al., *Pharm Res.*, 21(12): 2377-83 (2004)). Sodium thiosulfate has been reported to reduce the levels of light and temperature induced methionine-oxidation in rhuMab HER2; however, the formation of a thiosulfate-protein adduct was also reported in this study (Lam XM, Yang JY, et al., *J Pharm Sci.* 86(11): 1250-5 (1997)). Selection of an appropriate antioxidant is made according to the specific stresses and sensitivities of the protein.

[00123] Metal Ions

[00124] In general, transition metal ions are undesired in protein formulations because they can catalyze physical and chemical degradation reactions in proteins. However, specific metal ions are included in formulations when they are co-factors to proteins and in suspension formulations of proteins where they form coordination complexes (e.g., zinc suspension of insulin). Recently, the use of magnesium ions (10 –120 mM) has been proposed to inhibit the isomerization of aspartic acid to isoaspartic acid (WO 2004039337).

[00125] Two examples where metal ions confer stability or increased activity in proteins are human deoxyribonuclease (rhDNase, Pulmozyme®), and Factor VIII. In the case of rhDNase, Ca^{+2} ions (up to 100 mM) increased the stability of the enzyme through a specific binding site (Chen B, et al., *J Pharm Sci.*, 88(4): 477-82 (1999)). In fact, removal of calcium ions from the solution with EGTA caused an increase in deamidation and aggregation. However, this effect was observed only with Ca^{+2} ions; other divalent cations – Mg^{+2}, Mn^{+2} and Zn^{+2} were observed to destabilize rhDNase. Similar effects were observed in Factor VIII. Ca^{+2} and Sr^{+2} ions stabilized the protein while others like Mg^{+2}, Mn^{+2} and Zn^{+2}, Cu^{+2} and Fe^{+2} destabilized the enzyme (Fatouros, A., et al., *Int. J. Pharm.*, 155, 121–131 (1997). In a separate study with Factor VIII, a significant increase in aggregation rate was observed in the presence of Al^{+3} ions (Derrick TS, et al., *J. Pharm. Sci.*, 93(10): 2549-57 (2004)). The authors note that other excipients like buffer salts are often contaminated with

Al^{+3} ions and illustrate the need to use excipients of appropriate quality in formulated products.

[00126] Preservatives

[00127] Preservatives are necessary when developing multi-use parenteral formulations that involve more than one extraction from the same container. Their primary function is to inhibit microbial growth and ensure product sterility throughout the shelf-life or term of use of the drug product. Commonly used preservatives include benzyl alcohol, phenol and m-cresol. Although preservatives have a long history of use, the development of protein formulations that includes preservatives can be challenging. Preservatives almost always have a destabilizing effect (aggregation) on proteins, and this has become a major factor in limiting their use in multi-dose protein formulations (Roy S, et al., *J Pharm Sci.*, 94(2): 382-96 (2005)).

[00128] To date, most protein drugs have been formulated for single-use only. However, when multi-dose formulations are possible, they have the added advantage of enabling patient convenience, and increased marketability. A good example is that of human growth hormone (hGH) where the development of preserved formulations has led to commercialization of more convenient, multi-use injection pen presentations. At least four such pen devices containing preserved formulations of hGH are currently available on the market. Norditropin® (liquid, Novo Nordisk), Nutropin AQ® (liquid, Genentech) & Genotropin (lyophilized – dual chamber cartridge, Pharmacia & Upjohn) contain phenol while Somatrope® (Eli Lilly) is formulated with m-cresol.

[00129] Several aspects need to be considered during the formulation development of preserved dosage forms. The effective preservative concentration in the drug product must be optimized. This requires testing a given preservative in the dosage form with concentration ranges that confer anti-microbial effectiveness without compromising protein stability. For example, three preservatives were successfully screened in the development of a liquid formulation for interleukin-1 receptor (Type I), using differential scanning calorimetry (DSC). The preservatives were rank ordered based on their impact on stability at concentrations commonly used in marketed products (Remmele RL Jr., et al., *Pharm Res.*, 15(2): 200-8 (1998)).

[00130] As might be expected, development of liquid formulations containing preservatives are more challenging than lyophilized formulations. Freeze-dried products can be lyophilized without the preservative and reconstituted with a preservative containing diluent at the time of use. This shortens the time for which a preservative is in contact with

the protein significantly minimizing the associated stability risks. With liquid formulations, preservative effectiveness and stability have to be maintained over the entire product shelf-life (~ 18 –24 months). An important point to note is that preservative effectiveness has to be demonstrated in the final formulation containing the active drug and all excipient components.

[00131] Some preservatives can cause injection site reactions, which is another factor that needs consideration when choosing a preservative. In clinical trials that focused on the evaluation of preservatives and buffers in Norditropin, pain perception was observed to be lower in formulations containing phenol and benzyl alcohol as compared to a formulation containing m-cresol (Kappelgaard A.M., *Horm Res*. 62 Suppl 3:98-103 (2004)). Interestingly, among the commonly used preservative, benzyl alcohol possesses anesthetic properties (Minogue SC, and Sun DA., *Anesth Analg*., 100(3): 683-6 (2005)).

[00132] Given the teachings and guidance provided herein, those skilled in the art will know what amount or range of excipient can be included in any particular formulation to achieve a biopharmaceutical formulation of the invention that promotes retention in stability of the biopharmaceutical. For example, the amount and type of a salt to be included in a biopharmaceutical formulation of the invention can be selected based on to the desired osmolality (i.e., isotonic, hypotonic or hypertonic) of the final solution as well as the amounts and osmolality of other components to be included in the formulation. Similarly, by exemplification with reference to the type of polyol or sugar included in a formulation, the amount of such an excipient will depend on its osmolality.

[00133] By way of example, inclusion of about 5% sorbitol can achieve isotonicity while about 9% of a sucrose excipient is needed to achieve isotonicity. Selection of the amount or range of concentrations of one or more excipients that can be included within a biopharmaceutical formulation of the invention has been exemplified above by reference to salts, polyols and sugars. However, those skilled in the art will understand that the considerations described herein and further exemplified by reference to specific excipients are equally applicable to all types and combinations of excipients including, for example, salts, amino acids, other tonicity agents, surfactants, stabilizers, bulking agents, cryoprotectants, lyoprotectants, anti-oxidants, metal ions, chelating agents and/or preservatives.

[00134] Further, where a particular excipient is reported in a formulation by, e.g., percent (%) w/v, those skilled in the art will recognize that the equivalent molar concentration of that excipient is also contemplated.

[00135] Of course, a person having ordinary skill in the art would recognize that the concentrations of the aforementioned excipients share an interdependency within a particular formulation. By way of example, the concentration of a bulking agent may be lowered where, e.g., there is a high protein/peptide concentration or where, e.g., there is a high stabilizing agent concentration. In addition, a person having ordinary skill in the art would recognize that, in order to maintain the isotonicity of a particular formulation in which there is no bulking agent, the concentration of a stabilizing agent would be adjusted accordingly (i.e., a "tonicifying" amount of stabilizer would be used).

[00136] The compositions are stable for at least two years at 2°C to 8°C in the lyophilized state. This long-term stability is beneficial for extending the shelf life of the pharmaceutical product.

[00137] Methods of Preparation

[00138] The present invention further contemplates methods for the preparation of therapeutic protein formulations. In one aspect, methods for preparing a lyophilized therapeutic peptibody formulation comprising the step of lyophilizing a therapeutic peptibody composition in a buffer comprising a buffering agent, a bulking agent, a stabilizing agent and a surfactant;

[00139] The present methods further comprise one or more of the following steps: adding a stabilizing agent to said mixture prior to lyophilizing, adding at least one agent selected from a bulking agent, an osmolarity regulating agent, and a surfactant to said mixture prior to lyophilization. The bulking agent may be any bulking agent described herein. In one aspect, the bulking agent is mannitol. In another embodiment, the stabilizing agent is sucrose. The surfactant may be any surfactant described herein. In one embodiment, the surfactant is polysorbate-20.

[00140] The standard reconstitution practice for lyophilized material is to add back a volume of pure water or sterile water for injection (WFI) (typically equivalent to the volume removed during lyophilization), although dilute solutions of antibacterial agents are sometimes used in the production of pharmaceuticals for parenteral administration [Chen, Drug Development and Industrial Pharmacy, 18:1311-1354 (1992)]. Accordingly, methods are provided for preparation of reconstituted therapeutic peptibodies comprising the step of adding a diluent to a lyophilized therapeutic peptibody composition of the invention.

[00141] The lyophilized therapeutic peptibody composition may be reconstituted as an aqueous solution. A variety of aqueous carriers, e.g., sterile water for injection, water with preservatives for multi dose use, or water with appropriate amounts of surfactants (for

example, polysorbate-20), 0.4% saline, 0.3% glycine, or aqueous suspensions may contain the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions. In various aspects, such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate.

[00142] To administer compositions to human or test animals, in one aspect, the compositions comprises one or more pharmaceutically acceptable carriers. The phrases "pharmaceutically" or "pharmacologically acceptable" refer to molecular entities and compositions that are stable, inhibit protein degradation such as aggregation and cleavage products, and in addition do not produce allergic, or other adverse reactions when administered using routes well-known in the art, as described below. "Pharmaceutically acceptable carriers" include any and all clinically useful solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like, including those agents disclosed above.

[00143] The therapeutic peptibody compositions may be administered orally, topically, transdermally, parenterally, by inhalation spray, vaginally, rectally, or by intracranial injection. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intracisternal injection, or infusion techniques. Administration by intravenous, intradermal, intramusclar, intramammary, intraperitoneal, intrathecal, retrobulbar, intrapulmonary injection and or surgical implantation at a particular site is contemplated as well. Generally, compositions are essentially free of pyrogens, as well as other impurities that could be harmful to the recipient.

[00144] Single or multiple administrations of the compositions can be carried out with the dose levels and pattern being selected by the treating physician. For the prevention or treatment of disease, the appropriate dosage will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether drug is administered for

preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the drug, and the discretion of the attending physician.

[00145] **Kits**

[00146] As an additional aspect, the invention includes kits which comprise one or more lyophilized compounds or compositions packaged in a manner which facilitates their use for administration to subjects. In one embodiment, such a kit includes a compound or composition described herein (e.g., a composition comprising a therapeutic protein or peptide), packaged in a container such as a sealed bottle or vessel, with a label affixed to the container or included in the package that describes use of the compound or composition in practicing the method. In one embodiment, the kit contains a first container having a lyophilized therapeutic protein or peptide composition and a second container having a physiologically acceptable reconstitution solution for the lyophilized composition. In one aspect, the compound or composition is packaged in a unit dosage form. The kit may further include a device suitable for administering the composition according to a specific route of administration. Preferably, the kit contains a label that describes use of the therapeutic protein or peptide composition.

[00147] **Dosages**

[00148] The dosage regimen involved in a method for treating a condition described herein 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. In various aspects, the daily regimen is in the range of 0.1-1000 μg of a preparation per kilogram of body weight (calculating the mass of the protein alone, without chemical modification) or 0.1-150 μg/kg. In some embodiments of the invention, the dose may exceed 1mg/kg, 3 mg/kg, or 10 mg/kg.

[00149] Preparations of the invention may be administered by an initial bolus followed by a continuous infusion to maintain therapeutic circulating levels of drug product. As another example, the inventive compound may be administered as a one-time dose. Those of ordinary skill in the art will readily optimize effective dosages and administration regimens as determined by good medical practice and the clinical condition of the individual patient. The frequency of dosing will depend on the pharmacokinetic parameters of the agents and the route of administration. The optimal pharmaceutical formulation will be determined by one skilled in the art depending upon the route of administration and desired dosage. See for example, Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co.,

Easton, PA 18042) pages 1435-1712, the disclosure of which is hereby incorporated by reference. Such formulations may influence the physical state, stability, rate of *in vivo* release, and rate of *in vivo* clearance of the administered agents. Depending on the route of administration, a suitable dose may be calculated according to body weight, body surface area or organ size. Further refinement of the calculations necessary to determine the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art without undue experimentation, especially in light of the dosage information and assays disclosed herein, as well as the pharmacokinetic data observed in the human clinical trials discussed above. Appropriate dosages may be ascertained through use of established assays for determining blood level dosages in conjunction with appropriate dose-response data. The final dosage regimen will be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the drug's specific activity, the severity of the damage and the responsiveness of the patient, the age, condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. As studies are conducted, further information will emerge regarding the appropriate dosage levels and duration of treatment for various diseases and conditions.

[00150] **Structure of compounds**

[00151] In General. In preparations in accordance with the invention, a peptide is attached to a vehicle through the N-terminus of the peptide, C-terminus of the peptide, or both, and the resulting structure may be further modified with a covalently attached WSP which is attached to the vehicle moiety in the vehicle-peptide product. Thus, the therapeutic peptibody molecules of this invention may be described by the following formula I:

I $$[(X^1)_a\text{-}F^1\text{-}(X^2)_b]\text{-}(L^1)_c\text{-}WSP_d$$

wherein:

F^1 is a vehicle;

X^1 is selected from

$P^1\text{-}(L^2)_e\text{-}$

$P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$

$P^3\text{-}(L^4)_g\text{-}P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$ and

$P^4\text{-}(L^5)_h\text{-}P^3\text{-}(L^4)_g\text{-}P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$

X^2 is selected from:

$-(L^2)_e-P^1$,

$-(L^2)_e-P^1-(L^3)_f-P^2$,

$-(L^2)_e-P^1-(L^3)_f-P^2-(L^4)_g-P^3$, and

$-(L^2)_e-P^1-(L^3)_f-P^2-(L^4)_g-P^3-(L^5)_h-P^4$

wherein P^1, P^2, P^3, and P^4 are each independent sequences of pharmacologically active peptides;

L^1, L^2, L^3, L^4, and L^5 are each independently linkers;

a, b, c, e, f, g, and h are each independently 0 or 1,

provided that at least one of a and b is 1;

d is 0, 1, or greater than 1; and

WSP is a water soluble polymer, the attachment of which is effected at any reactive moiety in F^1.

[00152] Thus, compound I comprises compounds of the formulae

II $[X^1-F^1]-(L^1)_c-WSP_d$

including multimers thereof, wherein F^1 is an Fc domain and is attached at the C-terminus of X^1, and one or more WSP is attached to the Fc domain, optionally through linker L^1;

III $[F^1-X^2]-(L^1)_c-WSP_d$

including multimers thereof, wherein F^1 is an Fc domain and is attached at the N-terminus of X^2, and one or more WSP is attached to the Fc domain, optionally through linker L^1;

IV $[F^1-(L^1)_c-P^1]-(L^1)_c-WSP_d$

including multimers thereof, wherein F^1 is an Fc domain and is attached at the N-terminus of $-(L^1)_c-P^1$ and one or more WSP is attached to the Fc domain, optionally through linker L^1; and

V $[F^1-(L^1)_e-P^1-(L^2)_f-P^2]-(L^1)_c-WSP_d$

including multimers thereof, wherein F^1 is an Fc domain and is attached at the N-terminus of $-L^1-P^1-L^2-P^2$ and one or more WSP is attached to the Fc domain, optionally through linker L^1.

[00153] In one embodiment, F^1 is an Fc domain and is attached to either the N-terminus or C-terminus of a peptide. In a related embodiment, the Fc is linked into a dimeric form as described herein to which 2 (or more) peptides are attached. The peptides may be homodimeric (i.e., the same amino acid sequence), or heterodynammic (i.e., different amino acid sequences that bind the same target or that bind different targets).

[00154] In another embodiment, Fc-Loops comprising a peptide(s) are provided. Fc-Loops comprising a peptide(s) are prepared in a process in which at least one biologically active peptide is incorporated as an internal sequence into an 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 added need not correspond to the number of amino acids removed from the previously existing Fc domain. For example, in one aspect, a molecule in which 10 amino acids are removed and 15 amino acids are added is provided. Pharmacologically active compounds provided are 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 as an internal sequence 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, e.g., as described in U.S. Pat. App. Nos. 2003/0195156, 2003/0176352, 2003/0229023, and 2003/0236193, and international publication numbers WO 00/24770 and WO 04/026329. The process described in U.S. Patent Application Publication No. US2006/0140934 may also be employed to modify an Fc domain that is part of an antibody. 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. Molecules comprising an internal peptide sequence are also referred to as "Fc internal peptibodies" or "Fc internal peptide molecules."

[00155] 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.

[00156] 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.

[00157] A use contemplated for Fc internal peptide molecules is as a therapeutic or a prophylactic agent. 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.

[00158] Peptides. Any number of peptides may be used in conjunction with the present invention. Of particular interest are peptides that mimic the activity of EPO, TPO, growth hormone, G-CSF, GM-CSF, IL-1ra, CTLA4, TRAIL, TNF, VEGF, MMP, myostatin, integrin, OPG, OPG-L, NGF, TALL-1, Ang-2 binding partner(s), TGF-α, and TGF-β. Peptide antagonists are also of interest, particularly those antagonistic to the activity of TNF, any of the interleukins (IL-1, 2, 3, ...), and proteins involved in complement activation (e.g., C3b). Targeting peptides are also of interest, including tumor-homing peptides, membrane-transporting peptides, and the like. All of these classes of peptides may be discovered by methods described in the references cited in this specification and other references.

[00159] 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.

[00160] By way of example and without limitation, a group of peptides that bind to cytokine receptors are provided. 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 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 2. IL-3, IL-5, GM-CSF 3. IL-6, IL-11, IL-12, LIF, OSM, CNTF, Leptin (OB) 4. G-CSF, EPO, TPO, PRL, GH 5. IL-17, HVS-IL-17	I. Cytokine R (CKR)	1. shared γCr, IL-9R, IL-4R 2. shared GP 140 βR 3. 3.shared RP 130, IL-6 R, Leptin R 4. "single chain" R, GCSF-R, TPO-R, GH-R 5. other R[2]
II. IL-10 ligands	IL-10, BCRF-1, HSV-IL-10	II. IL-10 R	
III. Interferons	1. IFN-αl, α2, α4, m, t, IFN-β[3] 2. IFN-γ	III. Interferon R	1. IFNAR 2. IFNGR
IV. IL-1 and IL-1 like ligands	1. IL-1α, IL-1β, IL-1Ra 2. IL-18, IL-18BP	IV. IL-1R	1. IL-1R, IL-1RAcP 2. IL-18R, IL-18RAcP
V. TNF family	1. TNF-α, TNF-β (LT), FASL, CD40 L, CD30L, CD27 L, OX40L, OPGL, TRAIL, APRIL, AGP-3, BLys, TL5, Ntn-2, KAY, Neutrokine-α	3. NGF/TNF R[4]	TNF-RI, AGP-3R, DR4, DR5, OX40, OPG, TACI, CD40, FAS, ODR
VI. Chemokines	1. α chemokines:	4. Chemokine R	1. CXCR

[1] IL-17R - belongs to CKR family but is unassigned to 4 indicated subjamilies.
[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-DR 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.

	IL-8, GRO α, β, γ, IF-10, PF-4, SDF-1 2. β chemokines: MIP1α, MIP1β, MCP-1,2,3,4, RANTES, eotaxin 3. γ chemokines: lymphotactin		2. CCR 3. CR 4. DARC[5]
VII. Growth factors	1.1 SCF, M-CSF, PDGF-AA, AB, BB, KDR, FLT-1, FLT-3L, VEGF, SSV-PDGF, HGF, SF 1.2 FGFα, FGFβ 1.3 EGF, TGF-α, VV-F19 (EGF-like) 1.4 IGF-I, IGF-II, Insulin 1.5 NGF, BDNF, NT-3, NT-4[6] 2. TGF-β1,β2,β3	VII. RKF	1. TK sub-family 1.1 IgTK III R, VEGF-RI, VEGF-RII 1.2 IgTK IV R 1.3 Cysteine-rich TK-I 1.4 Cysteine rich TK-II, IGF-RI 1.5 Cysteine knot TK V 2. Serine-threonine kinase subfamily (STKS)[7]

[00161] Other proteins of interest as targets for peptide generation in the present invention include the following:

αvβ3

αVβ1

Ang-2

B7

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

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

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

B7RP1

CRP1

Calcitonin

CD28

CETP

cMet

Complement factor B

C4b

CTLA4

Glucagon

Glucagon Receptor

LIPG

MPL

splice variants of molecules preferentially expressed on tumor cells; e.g., CD44, CD30

unglycosylated variants of mucin and Lewis Y surface glycoproteins

CD19, CD20, CD33, CD45

prostate specific membrane antigen and prostate specific cell antigen

matrix metalloproteinases (MMPs), both secreted and membrane-bound (e.g., MMP-9)

Cathepsins

TIE-2 receptor

heparanase

urokinase plasminogen activator (UPA), UPA receptor

parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), PTH-RI, PTH-RII

Her2

Her3

Insulin

Myostatin

TALL-1

Nerve growth factor

Integrins and receptors

Selectins and receptors thereof

Cell adhesion molecules and receptors thereof

[00162] Exemplary peptides appear in Tables 4 through 38 below. These peptides may be prepared by any methods disclosed in the art, many of which are discussed herein. In most tables that follow, single letter amino acid abbreviations are used. The "X" in these sequences (and throughout this specification, unless specified otherwise in a particular instance) means that any of the 20 naturally occurring amino acid residues may be present. Any of these peptides may be linked in tandem (i.e., sequentially), with or without linkers, and a few tandem-linked examples are provided in the table. Linkers are listed as "Λ" and may be any of the linkers described herein. Tandem repeats and linkers are shown separated by dashes for clarity. Any peptide containing a cysteinyl residue may be cross-linked with another Cys-containing peptide, either or both of which may be linked to a vehicle. A few cross-linked examples are provided in the table. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well; see, for example, EPO-mimetic peptides in Table 5. A few examples of intrapeptide disulfide-bonded peptides are specified in the table. Any of these peptides may be derivatized as described herein, and a few derivatized examples are provided in the table. Derivatized peptides in the tables are exemplary rather than limiting, as the associated underivatized peptides may be employed in this invention, as well. For derivatives in which the carboxyl terminus may be capped with an amino group, the capping amino group is shown as $-NH_2$. For derivatives in which amino acid residues are substituted by moieties other than amino acid residues, the substitutions are denoted by σ, which signifies any of the moieties described in Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9 and Cuthbertson et al. (1997), J. Med. Chem. 40: 2876-82, which are incorporated by reference. The J substituent and the Z substituents (Z_5, Z_6, ...Z_{40}) are as defined in U.S. Pat. Nos. 5,608,035 ,5,786,331, and 5,880,096, which are incorporated by reference. For the EPO-mimetic sequences (Table 5), the substituents X_2 through X_{11} and the integer "n" are as defined in WO 96/40772, which is incorporated by reference. Also for the EPO-mimetic sequences, the substituents X_{na}, X_{1a}, X_{2a}, X_{3a}, X_{4a}, X_{5a} and X_{ca} follow the definitions of X_n, X_1, X_2, X_3, X_4, X_5, and X_c, respectively, of WO 99/47151, which is also incorporated by reference. The substituents "Ψ," "Θ," and "+" are as defined in Sparks et al. (1996), Proc. Natl. Acad. Sci. 93: 1540-4, which is hereby incorporated by reference. X_4, X_5, X_6, and X_7 are as defined in U.S. Pat. No. 5,773,569, which is hereby incorporated by reference, except that: for integrin-binding peptides, X_1, X_2, X_3, X_4, X_5, X_6, X_7, and X_8 are as defined in International applications WO 95/14714, published June 1, 1995 and WO 97/08203, published March 6, 1997, which are also incorporated by reference; and for VIP-

mimetic peptides, X_1, X_1', X_1'', X_2, X_3, X_4, X_5, X_6 and Z and the integers m and n are as defined in WO 97/40070, published October 30, 1997, which is also incorporated by reference. Xaa and Yaa below are as defined in WO 98/09985, published March 12, 1998, which is incorporated by reference. AA_1, AA_2, AB_1, AB_2, and AC are as defined in International application WO 98/53842, published December 3, 1998, which is incorporated by reference. X^1, X^2, X^3, and X^4 in Table 17 only are as defined in European application EP 0 911 393, published April 28, 1999. Residues appearing in boldface are D-amino acids. All peptides are linked through peptide bonds unless otherwise noted. Abbreviations are listed at the end of this specification. In the "SEQ ID NO." column, "NR" means that no sequence listing is required for the given sequence.

Table 4—IL-1 antagonist peptide sequences

Sequence/structure	**SEQ ID NO:**
$Z_{11}Z_7Z_8QZ_5YZ_6Z_9Z_{10}$	3
$XXQZ_5YZ_6XX$	4
$Z_7XQZ_5YZ_6XX$	5
$Z_7Z_8QZ_5YZ_6Z_9Z_{10}$	6
$Z_{11}Z_7Z_8QZ_5YZ_6Z_9Z_{10}$	7
$Z_{12}Z_{13}Z_{14}Z_{15}Z_{16}Z_{17}Z_{18}Z_{19}Z_{20}Z_{21}Z_{22}Z_{11}Z_7Z_8QZ_5YZ_6Z_9Z_{10}L$	8
$Z_{23}NZ_{24}Z_{39}Z_{25}Z_{26}Z_{27}Z_{28}Z_{29}Z_{30}Z_{40}$	9
TANVSSFEWTPYYWQPYALPL	10
SWTDYGYWQPYALPISGL	11
ETPFTWEESNAYYWQPYALPL	12
ENTYSPNWADSMYWQPYALPL	13
SVGEDHNFWTSEYWQPYALPL	14
DGYDRWRQSGERYWQPYALPL	15
FEWTPGYWQPY	16
FEWTPGYWQHY	17
FEWTPGWYQJY	18
AcFEWTPGWYQJY	19
FEWTPGWpYQJY	20
FAWTPGYWQJY	21
FEWAPGYWQJY	22
FEWVPGYWQJY	23
FEWTPGYWQJY	24
AcFEWTPGYWQJY	25

FEWTPaWYQJY	26
FEWTPSarWYQJY	27
FEWTPGYYQPY	28
FEWTPGWWQPY	29
FEWTPNYWQPY	30
FEWTPvYWQJY	31
FEWTPecGYWQJY	32
FEWTPAibYWQJY	33
FEWTSarGYWQJY	34
FEWTPGYWQPY	35
FEWTPGYWQHY	36
FEWTPGWYQJY	37
AcFEWTPGWYQJY	38
FEWTPGW-pY-QJY	39
FAWTPGYWQJY	40
FEWAPGYWQJY	41
FEWVPGYWQJY	42
FEWTPGYWQJY	43
AcFEWTPGYWQJY	44
FEWTPAWYQJY	45
FEWTPSarWYQJY	46
FEWTPGYYQPY	47
FEWTPGWWQPY	48
FEWTPNYWQPY	49
FEWTPVYWQJY	50
FEWTPecGYWQJY	51
FEWTPAibYWQJY	52
FEWTSarGYWQJY	53
FEWTPGYWQPYALPL	54
INapEWTPGYYQJY	55
YEWTPGYYQJY	56
FEWVPGYYQJY	57
FEWTPSYYQJY	58
FEWTPNYYQJY	59
TKPR	60
RKSSK	61
RKQDK	62
NRKQDK	63

RKQDKR	64
ENRKQDKRF	65
VTKFYF	66
VTKFY	67
VTDFY	68
SHLYWQPYSVQ	69
TLVYWQPYSLQT	70
RGDYWQPYSVQS	71
VHVYWQPYSVQT	72
RLVYWQPYSVQT	73
SRVWFQPYSLQS	74
NMVYWQPYSIQT	75
SVVFWQPYSVQT	76
TFVYWQPYALPL	77
TLVYWQPYSIQR	78
RLVYWQPYSVQR	79
SPVFWQPYSIQI	80
WIEWWQPYSVQS	81
SLIYWQPYSLQM	82
TRLYWQPYSVQR	83
RCDYWQPYSVQT	84
MRVFWQPYSVQN	85
KIVYWQPYSVQT	86
RHLYWQPYSVQR	87
ALVWWQPYSEQI	88
SRVWFQPYSLQS	89
WEQPYALPLE	90
QLVWWQPYSVQR	91
DLRYWQPYSVQV	92
ELVWWQPYSLQL	93
DLVWWQPYSVQW	94
NGNYWQPYSFQV	95
ELVYWQPYSIQR	96
ELMYWQPYSVQE	97
NLLYWQPYSMQD	98
GYEWYQPYSVQR	99
SRVWYQPYSVQR	100
LSEQYQPYSVQR	101

GGGWWQPYSVQR	102
VGRWYQPYSVQR	103
VHVYWQPYSVQR	104
QARWYQPYSVQR	105
VHVYWQPYSVQT	106
RSVYWQPYSVQR	107
TRVWFQPYSVQR	108
GRIWFQPYSVQR	109
GRVWFQPYSVQR	110
ARTWYQPYSVQR	111
ARVWWQPYSVQM	112
RLMFYQPYSVQR	113
ESMWYQPYSVQR	114
HFGWWQPYSVHM	115
ARFWWQPYSVQR	116
RLVYWQ PYAPIY	117
RLVYWQ PYSYQT	118
RLVYWQ PYSLPI	119
RLVYWQ PYSVQA	120
SRVWYQ PYAKGL	121
SRVWYQ PYAQGL	122
SRVWYQ PYAMPL	123
SRVWYQ PYSVQA	124
SRVWYQ PYSLGL	125
SRVWYQ PYAREL	126
SRVWYQ PYSRQP	127
SRVWYQ PYFVQP	128
EYEWYQ PYALPL	129
IPEYWQ PYALPL	130
SRIWWQ PYALPL	131
DPLFWQ PYALPL	132
SRQWVQ PYALPL	133
IRSWWQ PYALPL	134
RGYWQ PYALPL	135
RLLWVQ PYALPL	136
EYRWFQ PYALPL	137
DAYWVQ PYALPL	138
WSGYFQ PYALPL	139

NIEFWQ PYALPL	140
TRDWVQ PYALPL	141
DSSWYQ PYALPL	142
IGNWYQ PYALPL	143
NLRWDQ PYALPL	144
LPEFWQ PYALPL	145
DSYWWQ PYALPL	146
RSQYYQ PYALPL	147
ARFWLQ PYALPL	148
NSYFWQ PYALPL	149
RFMYWQPYSVQR	150
AHLFWQPYSVQR	151
WWQPYALPL	152
YYQPYALPL	153
YFQPYALGL	154
YWYQPYALPL	155
RWWQPYATPL	156
GWYQPYALGF	157
YWYQPYALGL	158
IWYQPYAMPL	159
SNMQPYQRLS	160
TFVYWQPY AVGLPAAETACN	161
TFVYWQPY SVQMTITGKVTM	162
TFVYWQPY SSHXXVPXGFPL	163
TFVYWQPY YGNPQWAIHVRH	164
TFVYWQPY VLLELPEGAVRA	165
TFVYWQPY VDYVWPIPIAQV	166
GWYQPYVDGWR	167
RWEQPYVKDGWS	168
EWYQPYALGWAR	169
GWWQPYARGL	170
LFEQPYAKALGL	171
GWEQPYARGLAG	172
AWVQPYATPLDE	173
MWYQPYSSQPAE	174
GWTQPYSQQGEV	175
DWFQPYSIQSDE	176
PWIQPYARGFG	177

RPLYWQPYSVQV	178
TLIYWQPYSVQI	179
RFDYWQPYSDQT	180
WHQFVQPYALPL	181
EWDS VYWQPYSVQ TLLR	182
WEQN VYWQPYSVQ SFAD	183
SDV VYWQPYSVQ SLEM	184
YYDG VYWQPYSVQ VMPA	185
SDIWYQ PYALPL	186
QRIWWQ PYALPL	187
SRIWWQ PYALPL	188
RSLYWQ PYALPL	189
TIIWEQ PYALPL	190
WETWYQ PYALPL	191
SYDWEQ PYALPL	192
SRIWCQ PYALPL	193
EIMFWQ PYALPL	194
DYVWQQ PYALPL	195
MDLLVQ WYQPYALPL	196
GSKVIL WYQPYALPL	197
RQGANI WYQPYALPL	198
GGGDEP WYQPYALPL	199
SQLERT WYQPYALPL	200
ETWVRE WYQPYALPL	201
KKGSTQ WYQPYALPL	202
LQARMN WYQPYALPL	203
EPRSQK WYQPYALPL	204
VKQKWR WYQPYALPL	205
LRRHDV WYQPYALPL	206
RSTASI WYQPYALPL	207
ESKEDQ WYQPYALPL	208
EGLTMK WYQPYALPL	209
EGSREG WYQPYALPL	210
VIEWWQ PYALPL	211
VWYWEQ PYALPL	212
ASEWWQ PYALPL	213
FYEWWQ PYALPL	214
EGWWVQ PYALPL	215

WGEWLQ PYALPL	216
DYVWEQ PYALPL	217
AHTWWQ PYALPL	218
FIEWFQ PYALPL	219
WLAWEQ PYALPL	220
VMEWWQ PYALPL	221
ERMWQ PYALPL	222
NXXWXX PYALPL	223
WGNWYQ PYALPL	224
TLYWEQ PYALPL	225
VWRWEQ PYALPL	226
LLWTQ PYALPL	227
SRIWXX PYALPL	228
SDIWYQ PYALPL	229
WGYYXX PYALPL	230
TSGWYQ PYALPL	231
VHPYXX PYALPL	232
EHSYFQ PYALPL	233
XXIWYQ PYALPL	234
AQLHSQ PYALPL	235
WANWFQ PYALPL	236
SRLYSQ PYALPL	237
GVTFSQ PYALPL	238
SIVWSQ PYALPL	239
SRDLVQ PYALPL	240
HWGH VYWQPYSVQ DDLG	241
SWHS VYWQPYSVQ SVPE	242
WRDS VYWQPYSVQ PESA	243
TWDA VYWQPYSVQ KWLD	244
TPPW VYWQPYSVQ SLDP	245
YWSS VYWQPYSVQ SVHS	246
YWY QPY ALGL	247
YWY QPY ALPL	248
EWI QPY ATGL	249
NWE QPY AKPL	250
AFY QPY ALPL	251
FLY QPY ALPL	252
VCK QPY LEWC	253

ETPFTWEESNAYYWQPYALPL	254
QGWLTWQDSVDMYWQPYALPL	255
FSEAGYTWPENTYWQPYALPL	256
TESPGGLDWAKIYWQPYALPL	257
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TANVSSFEWTPGYWQPYALPL	259
SVGEDHNFWTSE YWQPYALPL	260
MNDQTSEVSTFP YWQPYALPL	261
SWSEAFEQPRNL YWQPYALPL	262
QYAEPSALNDWG YWQPYALPL	263
NGDWATADWSNY YWQPYALPL	264
THDEHI YWQPYALPL	265
MLEKTYTTWTPG YWQPYALPL	266
WSDPLTRDADL YWQPYALPL	267
SDAFTTQDSQAM YWQPYALPL	268
GDDAAWRTDSLT YWQPYALPL	269
AIIRQLYRWSEM YWQPYALPL	270
ENTYSPNWADSM YWQPYALPL	271
MNDQTSEVSTFP YWQPYALPL	272
SVGEDHNFWTSE YWQPYALPL	273
QTPFTWEESNAY YWQPYALPL	274
ENPFTWQESNAY YWQPYALPL	275
VTPFTWEDSNVF YWQPYALPL	276
QIPFTWEQSNAY YWQPYALPL	277
QAPLTWQESAAY YWQPYALPL	278
EPTFTWEESKAT YWQPYALPL	279
TTTLTWEESNAY YWQPYALPL	280
ESPLTWEESSAL YWQPYALPL	281
ETPLTWEESNAY YWQPYALPL	282
EATFTWAESNAY YWQPYALPL	283
EALFTWKESTAY YWQPYALPL	284
STP-TWEESNAY YWQPYALPL	285
ETPFTWEESNAY YWQPYALPL	286
KAPFTWEESQAY YWQPYALPL	287
STSFTWEESNAY YWQPYALPL	288
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QTAFTWEESNAY YWQPYALPL	291

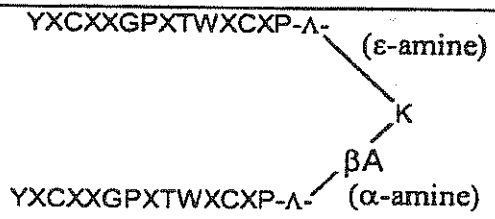
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FEWTPGYYQJYALPL	299
ETPFTWEESNAYYWQPYALPL	300
FTWEESNAYYWQJYALPL	301
ADVL YWQPYA PVTLWV	302
GDVAE YWQPYA LPLTSL	303
SWTDYG YWQPYA LPISGL	304
FEWTPGYWQPYALPL	305
FEWTPGYWQJYALPL	306
FEWTPGWYQPYALPL	307
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SWTDYGYWQPYALPISGL	312
ETPFTWEESNAYYWQPYALPL	313
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SVGEDHNFWTSEYWQPYALPL	315
DGYDRWRQSGERYWQPYALPL	316
FEWTPGYWQPYALPL	317
FEWTPGYWQPY	318
FEWTPGYWQJY	319
EWTPGYWQPY	320
FEWTPGWYQJY	321
AEWTPGYWQJY	322
FAWTPGYWQJY	323
FEATPGYWQJY	324
FEWAPGYWQJY	325
FEWTAGYWQJY	326
FEWTPAYWQJY	327
FEWTPGAWQJY	328
FEWTPGYAQJY	329

FEWTPGYWQJA	330
FEWTGGYWQJY	331
FEWTPGYWQJY	332
FEWTJGYWQJY	333
FEWTPecGYWQJY	334
FEWTPAibYWQJY	335
FEWTPSarWYQJY	336
FEWTSarGYWQJY	337
FEWTPNYWQJY	338
FEWTPVYWQJY	339
FEWTVPYWQJY	340
AcFEWTPGWYQJY	341
AcFEWTPGYWQJY	342
lNap-EWTPGYYQJY	343
YEWTPGYYQJY	344
FEWVPGYYQJY	345
FEWTPGYYQJY	346
FEWTPsYYQJY	347
FEWTPnYYQJY	348
SHLY-Nap-QPYSVQM	349
TLVY-Nap-QPYSLQT	350
RGDY-Nap-QPYSVQS	351
NMVY-Nap-QPYSIQT	352
VYWQPYSVQ	353
VY-Nap-QPYSVQ	354
TFVYWQJYALPL	355
FEWTPGYYQJ-Bpa	356
XaaFEWTPGYYQJ-Bpa	357
FEWTPGY-Bpa-QJY	358
AcFEWTPGY-Bpa-QJY	359
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AcFE-Bpa-TPGYYQJY	362
AcFE-Bpa-TPGYYQJY	363
Bpa-EWTPGYYQJY	364
AcBpa-EWTPGYYQJY	365
VYWQPYSVQ	366
RLVYWQPYSVQR	367

RLVY-Nap-QPYSVQR	368
RLDYWQPYSVQR	369
RLVWFQPYSVQR	370
RLVYWQPYSIQR	371
DNSSWYDSFLL	372
DNTAWYESFLA	373
DNTAWYENFLL	374
PARE DNTAWYDSFLI WC	375
TSEY DNTTWYEKFLA SQ	376
SQIP DNTAWYQSFLL HG	377
SPFI DNTAWYENFLL TY	378
EQIY DNTAWYDHFLL SY	379
TPFI DNTAWYENFLL TY	380
TYTY DNTAWYERFLM SY	381
TMTQ DNTAWYENFLL SY	382
TI DNTAWYANLVQ TYPQ	383
TI DNTAWYERFLA QYPD	384
HI DNTAWYENFLL TYTP	385
SQ DNTAWYENFLL SYKA	386
QI DNTAWYERFLL QYNA	387
NQ DNTAWYESFLL QYNT	388
TI DNTAWYENFLL NHNL	389
HY DNTAWYERFLQ QGWH	390
ETPFTWEESNAYYWQPYALPL	391
YIPFTWEESNAYYWQPYALPL	392
DGYDRWRQSGERYWQPYALPL	393
pY-lNap-pY-QJYALPL	394
TANVSSFEWTPGYWQPYALPL	395
FEWTPGYWQJYALPL	396
FEWTPGYWQPYALPLSD	397
FEWTPGYYQJYALPL	398
FEWTPGYWQJY	399
AcFEWTPGYWQJY	400
AcFEWTPGWYQJY	401
AcFEWTPGYYQJY	402
AcFEWTPaYWQJY	403
AcFEWTPaWYQJY	404
AcFEWTPaYYQJY	405

FEWTPGYYQJYALPL	406
FEWTPGYWQJYALPL	407
FEWTPGWYQJYALPL	408
TANVSSFEWTPGYWQPYALPL	409
AcFEWTPGYWQJY	410
AcFEWTPGWYQJY	411
AcFEWTPGYYQJY	412
AcFEWTPAYWQJY	413
AcFEWTPAWYQJY	414
AcFEWTPAYYQJY	415

Table 5—EPO-mimetic peptide sequences

Sequence/structure	SEQ ID NO:
YXCXXGPXTWXCXP	416
YXCXXGPXTWXCXP-YXCXXGPXTWXCXP	417
YXCXXGPXTWXCXP-Λ-YXCXXGPXTWXCXP	418
	419
GGTYSCHFGPLTWVCKPQGG	420
GGDYHCRMGPLTWVCKPLGG	421
GGVYACRMGPITWVCSPLGG	422
VGNYMCHFGPITWVCRPGGG	423
GGLYLCRFGPVTWDCGYKGG	424
GGTYSCHFGPLTWVCKPQGG- GGTYSCHFGPLTWVCKPQGG	425
GGTYSCHFGPLTWVCKPQGG -Λ- GGTYSCHFGPLTWVCKPQGG	426
GGTYSCHFGPLTWVCKPQGGSSK	427
GGTYSCHFGPLTWVCKPQGGSSK- GGTYSCHFGPLTWVCKPQGGSSK	428
GGTYSCHFGPLTWVCKPQGGSSK-Λ- GGTYSCHFGPLTWVCKPQGGSSK	429

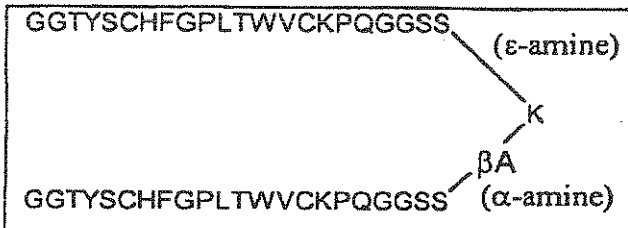
	430
GGTYSCHFGPLTWVCKPQGGSSK(Λ -biotin)	431
$CX_4X_5GPX_6TWX_7C$	432
GGTYSCHGPLTWVCKPQGG	433
VGNYMAHMGPITWVCRPGG	434
GGPHHVYACRMGPLTWIC	435
GGTYSCHFGPLTWVCKPQ	436
GGLYACHMGPMTWVCQPLRG	437
TIAQYICYMGPETWECRPSPKA	438
YSCHFGPLTWVCK	439
YCHFGPLTWVC	440
$X_3X_4X_5GPX_6TWX_7X_8$	441
$YX_2X_3X_4X_5GPX_6TWX_7X_8$	442
$X_1YX_2X_3X_4X_5GPX_6TWX_7X_8X_9X_{10}X_{11}$	443
$X_1YX_2CX_4X_5GPX_6TWX_7CX_9X_{10}X_{11}$	444
GGLYLCRFGPVTWDCGYKGG	445
GGTYSCHFGPLTWVCKPQGG	446
GGDYHCRMGPLTWVCKPLGG	447
VGNYMCHFGPITWVCRPGGG	448
GGVYACRMGPITWVCSPLGG	449
VGNYMAHMGPITWVCRPGG	450
GGTYSCHFGPLTWVCKPQ	451
GGLYACHMGPMTWVCQPLRG	452
TIAQYICYMGPETWECRPSPKA	453
YSCHFGPLTWVCK	454
YCHFGPLTWVC	455
SCHFGPLTWVCK	456
$(AX_2)_nX_3X_4X_5GPX_6TWX_7X_8$	457
$X_nCX_1X_2GWVGX_3CX_4X_5WX_C$	458

Table 6—TPO-mimetic peptide sequences

Sequence/structure	**SEQ ID NO:**
IEGPTLRQWLAARA	459

IEGPTLRQWLAAKA	460
IEGPTLREWLAARA	461
IEGPTLRQWLAARA-Λ-IEGPTLRQWLAARA	462
IEGPTLRQWLAAKA-Λ-IEGPTLRQWLAAKA	463
IEGPTLRQCLAARA-Λ-IEGPTLRQCLAARA |_____|	464
IEGPTLRQWLAARA-Λ-K(BrAc)-Λ-IEGPTLRQWLAARA	465
IEGPTLRQWLAARA-Λ-K(PEG)-Λ-IEGPTLRQWLAARA	466
IEGPTLRQCLAARA-Λ-IEGPTLRQWLAARA | IEGPTLRQCLAARA-Λ-IEGPTLRQWLAARA	467
IEGPTLRQWLAARA-Λ-IEGPTLRQCLAARA | IEGPTLRQWLAARA-Λ-IEGPTLRQCLAARA	468
VRDQIXXXL	469
TLREWL	470
GRVRDQVAGW	471
GRVKDQIAQL	472
GVRDQVSWAL	473
ESVREQVMKY	474
SVRSQISASL	475
GVRETVYRHM	476
GVREVIVMHML	477
GRVRDQIWAAL	478
AGVRDQILIWL	479
GRVRDQIMLSL	480
GRVRDQI$(X)_3$L	481
CTLRQWLQGC	482
CTLQEFLEGC	483
CTRTEWLHGC	484
CTLREWLHGGFC	485
CTLREWVFAGLC	486
CTLRQWLILLGMC	487
CTLAEFLASGVEQC	488
CSLQEFLSHGGYVC	489
CTLREFLDPTTAVC	490
CTLKEWLVSHEVWC	491
CTLREWL$(X)_{2\text{-}6}$C	492

REGPTLRQWM	493
EGPTLRQWLA	494
ERGPFWAKAC	495
REGPRCVMWM	496
CGTEGPTLSTWLDC	497
CEQDGPTLLEWLKC	498
CELVGPSLMSWLTC	499
CLTGPFVTQWLYEC	500
CRAGPTLLEWLTLC	501
CADGPTLREWISFC	502
$C(X)_{1-2}$EGPTLREWL$(X)_{1-2}$C	503
GGCTLREWLHGGFCGG	504
GGCADGPTLREWISFCGG	505
GNADGPTLRQWLEGRRPKN	506
LAIEGPTLRQWLHGNGRDT	507
HGRVGPTLREWKTQVATKK	508
TIKGPTLRQWLKSREHTS	509
ISDGPTLKEWLSVTRGAS	510
SIEGPTLREWLTSRTPHS	511

Table 7—G-CSF-mimetic peptide sequences

Sequence/structure	**SEQ ID NO:**
EEDCK	512
EEDCK | EEDCK	513
EEDσK	514
EEDσK | EEDσK	515
pGluEDσK	516
pGluEDσK | pGluEDσK	517
PicSDσK	518
PicSDσK |	519

PicSDσK	
EEDCK-Λ-EEDCK	520
EEDXK-Λ-EEDXK	521

Table 8—TNF-antagonist peptide sequences

Sequence/structure	SEQ ID NO:
YCFTASENHCY	522
YCFTNSENHCY	523
YCFTRSENHCY	524
FCASENHCY	525
YCASENHCY	526
FCNSENHCY	527
FCNSENRCY	528
FCNSVENRCY	529
YCSQSVSNDCF	530
FCVSNDRCY	531
YCRKELGQVCY	532
YCKEPGQCY	533
YCRKEMGCY	534
FCRKEMGCY	535
YCWSQNLCY	536
YCELSQYLCY	537
YCWSQNYCY	538
YCWSQYLCY	539
DFLPHYKNTSLGHRP	540
AA_1-AB_1 \ AC / AA_2-AB_2	NR

Table 9—Integrin-binding peptide sequences

Sequence/structure	SEQ ID NO:
$RX_1ETX_2WX_3$	541
$RX_1ETX_2WX_3$	542

RGDGX	543
CRGDGXC	544
$CX_1X_2RLDX_3X_4C$	545
CARRLDAPC	546
CPSRLDSPC	547
$X_1X_2X_3RGDX_4X_5X_6$	548
$CX_2CRGDCX_5C$	549
CDCRGDCFC	550
CDCRGDCLC	551
CLCRGDCIC	552
$X_1X_2DDX_4X_5X_7X_8$	553
$X_1X_2X_3DDX_4X_5X_6X_7X_8$	554
CWDDGWLC	555
CWDDLWWLC	556
CWDDGLMC	557
CWDDGWMC	558
CSWDDGWLC	559
CPDDLWWLC	560
NGR	NR
GSL	NR
RGD	NR
CGRECPRLCQSSC	561
CNGRCVSGCAGRC	562
CLSGSLSC	563
RGD	NR
NGR	NR
GSL	NR
NGRAHA	564
CNGRC	565
CDCRGDCFC	566
CGSLVRC	567
DLXXL	568
RTDLDSLRTYTL	569
RTDLDSLRTY	570
RTDLDSLRT	571
RTDLDSLR	572
GDLDLLKLRLTL	573
GDLHSLRQLLSR	574

RDDLHMLRLQLW	575
SSDLHALKKRYG	576
RGDLKQLSELTW	577
RGDLAALSAPPV	578

Table 10—Selectin antagonist peptide sequences

Sequence/structure	SEQ ID NO:
DITWDQLWDLMK	579
DITWDELWKIMN	580
DYTWFELWDMMQ	581
QITWAQLWNMMK	582
DMTWHDLWTLMS	583
DYSWHĐLWEMMS	584
EITWDQLWEVMN	585
HVSWEQLWDIMN	586
HITWDQLWRIMT	587
RNMSWLELWEHMK	588
AEWTWDQLWHVMNPAESQ	589
HRAEWLALWEQMSP	590
KKEDWLALWRIMSV	591
ITWDQLWDLMK	592
DITWDQLWDLMK	593
DITWDQLWDLMK	594
DITWDQLWDLMK	595
CQNRYTDLVAIQNKNE	596
AENWADNEPNNKRNNED	597
RKNNKTWTWVGTKKALTNE	598
KKALTNEAENWAD	599
CQXRYTDLVAIQNKXE	600
RKXNXXWTWVGTXKXLTEE	601
AENWADGEPNNKXNXED	602
CXXXYTXLVAIQNKXE	603
RKXXXXWXWVGTXKXLTXE	604
AXNWXXXEPNNXXXED	605
XKXXKTXEAXNWXX	606

Table 11—Antipathogenic peptide sequences

Sequence/structure	SEQ ID NO:
GFFALIPKIISSPLFKTLLSAVGSALSSSGGQQ	607
GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE	608
GFFALIPKIISSPLFKTLLSAV	609
GFFALIPKIISSPLFKTLLSAV	610
KGFFALIPKIISSPLFKTLLSAV	611
KKGFFALIPKIISSPLFKTLLSAV	612
KKGFFALIPKIISSPLFKTLLSAV	613
GFFALIPKIIS	614
GIGAVLKVLTTGLPALISWIKRKRQQ	615
GIGAVLKVLTTGLPALISWIKRKRQQ	616
GIGAVLKVLTTGLPALISWIKRKRQQ	617
GIGAVLKVLTTGLPALISWIKR	618
AVLKVLTTGLPALISWIKR	619
KLLLLLKLLLLK	620
KLLLKLLLKLLK	621
KLLLKLKLKLLK	622
KKLLKLKLKLKK	623
KLLLKLLLKLLK	624
KLLLKLKLKLLK	625
KLLLLK	626
KLLLKLLK	627
KLLLKLKLKLLK	628
KLLLKLKLKLLK	629
KLLLKLKLKLLK	630
KAAAKAAAKAAK	631
KVVVKVVVKVVK	632
KVVVKVKVKVVK	633
KVVVKVKVKVK	634
KVVVKVKVKVVK	635
KLILKL	636
KVLHLL	637
LKLRLL	638
KPLHLL	639
KLILKLVR	640
KVFHLLHL	641
HKFRILKL	642

KPFHILHL	643
KIIIKIKIKIIK	644
KIIIKIKIKIIK	645
KIIIKIKIKIIK	646
KIPIKIKIKIPK	647
KIPIKIKIKIVK	648
RIIIRIRIRIIR	649
RIIIRIRIRIIR	650
RIIIRIRIRIIR	651
RIVIRIRIRLIR	652
RIIVRIRLRIIR	653
RIGIRLRVRIIR	654
KIVIRIRIRLIR	655
RIAVKWRLRFIK	656
KIGWKLRVRIIR	657
KKIGWLIIRVRR	658
RIVIRIRIRLIRIR	659
RIIVRIRLRIIRVR	660
RIGIRLRVRIIRRV	661
KIVIRIRARLIRIRIR	662
RIIVKIRLRIIKKIRL	663
KIGIKARVRIIRVKII	664
RIIVHIRLRIIHHIRL	665
HIGIKAHVRIIRVHII	666
RIYVKIHLRYIKKIRL	667
KIGHKARVHIIRYKII	668
RIYVKPHPRYIKKIRL	669
KPGHKARPHIIRYKII	670
KIVIRIRIRLIRIRIRKIV	671
RIIVKIRLRIIKKIRLIKK	672
KIGWKLRVRIIRVKIGRLR	673
KIVIRIRIRLIRIRIRKIVKVKRIR	674
RFAVKIRLRIIKKIRLIKKIRKRVIK	675
KAGWKLRVRIIRVKIGRLRKIGWKKRVRIK	676
RIYVKPHPRYIKKIRL	677
KPGHKARPHIIRYKII	678
KIVIRIRIRLIRIRIRKIV	679
RIIVKIRLRIIKKIRLIKK	680

RIYVSKISIYIKKIRL	681
KIVIFTRIRLTSIRIRSIV	682
KPIHKARPTIIRYKMI	683
cyclicCKGFFALIPKIISSPLFKTLLSAVC	684
CKKGFFALIPKIISSPLFKTLLSAVC	685
CKKKGFFALIPKIISSPLFKTLLSAVC	686
CyclicCRIVIRIRIRLIRIRC	687
CyclicCKPGHKARPHIIRYKIIC	688
CyclicCRFAVKIRLRIIKKIRLIKKIRKRVIKC	689
KLLLKLLL KLLKC	690
KLLLKLLLKLLK	691
KLLLKLKLKLLKC	692
KLLLKLLLKLLK	693

Table 12—VIP-mimetic peptide sequences

Sequence/structure	**SEQ ID NO:**
HSDAVFYDNYTR LRKQMAVKKYLN SILN	694
Nle HSDAVFYDNYTR LRKQMAVKKYLN SILN	695
X_1 X_1' X_1'' X_2	696
X_3 S X_4 LN	697
NH CH CO KKYX5 NH CH CO X6 | | (CH2)m___Z_____(CH2)n	698
KKYL	699
NSILN	700
KKYL	701
KKYA	702
AVKKYL	703
NSILN	704
KKYV	705
SILauN	706
KKYLNle	707
NSYLN	708
NSIYN	709
KKYLPPNSILN	710
LauKKYL	711
CapKKYL	712

KYL	713
KKYNle	714
VKKYL	715
LNSILN	716
YLNSILN	717
KKYLN	718
KKYLNS	719
KKYLNSI	720
KKYLNSIL	721
KKYL	722
KKYDA	723
AVKKYL	724
NSILN	725
KKYV	726
SILauN	727
NSYLN	728
NSIYN	729
KKYLNle	730
KKYLPPNSILN	731
KKYL	732
KKYDA	733
AVKKYL	734
NSILN	735
KKYV	736
SILauN	737
LauKKYL	738
CapKKYL	739
KYL	740
KYL	741
KKYNle	742
VKKYL	743
LNSILN	744
YLNSILN	745
KKYLNle	746
KKYLN	747
KKYLNS	748
KKYLNSI	749
KKYLNSIL	750

KKKYLD	751
cyclicCKKYLC	752
CKKYLK | | S-CH_2-CO	753
KKYA	754
WWTDTGLW	755
WWTDDGLW	756
WWDTRGLWVWTI	757
FWGNDGIWLESG	758
DWDQFGLWRGAA	759
RWDDNGLWVVVL	760
SGMWSHYGIWMG	761
GGRWDQAGLWVA	762
KLWSEQGIWMGE	763
CWSMHGLWLC	764
GCWDNTGIWVPC	765
DWDTRGLWVY	766
SLWDENGAWI	767
KWDDRGLWMH	768
QAWNERGLWT	769
QWDTRGLWVA	770
WNVHGIWQE	771
SWDTRGLWVE	772
DWDTRGLWVA	773
SWGRDGLWIE	774
EWTDNGLWAL	775
SWDEKGLWSA	776
SWDSSGLWMD	777

Table 13—Mdm/hdm antagonist peptide sequences

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

MPRFMDYWEGLN	783
VQNFIDYWTQQF	784
TGPAFTHYWATF	785
IDRAPTFRDHWFALV	786
PRPALVFADYWETLY	787
PAFSRFWSDLSAGAH	788
PAFSRFWSKLSAGAH	789
PXFXDYWXXL	790
QETFSDLWKLLP	791
QPTFSDLWKLLP	792
QETFSDYWKLLP	793
QPTFSDYWKLLP	794

Table 14—Calmodulin antagonist peptide sequences

Sequence/structure	**SEQ ID NO:**
SCVKWGKKEFCGS	795
SCWKYWGKECGS	796
SCYEWGKLRWCGS	797
SCLRWGKWSNCGS	798
SCWRWGKYQICGS	799
SCVSWGALKLCGS	800
SCIRWGQNTFCGS	801
SCWQWGNLKICGS	802
SCVRWGQLSICGS	803
LKKFNARRKLKGAILTTMLAK	804
RRWKKNFIAVSAANRFKK	805
RKWQKTGHAVRAIGRLSS	806
INLKALAALAKKIL	807
KIWSILAPLGTTLVKLVA	808
LKKLLKLLKKLLKL	809
LKWKKLLKLLKKLLKKLL	810
AEWPSLTEIKTLSHFSV	811
AEWPSPTRVISTTYFGS	812
AELAHWPPVKTVLRSFT	813
AEGSWLQLLNLMKQMNN	814
AEWPSLTEIK	815

Table 15—Mast cell antagonists/Mast cell protease inhibitor peptide sequences

Sequence/structure	SEQ ID NO:
SGSGVLKRPLPILPVTR	816
RWLSSRPLPPLPLPPRT	817
GSGSYDTLALPSLPLHPMSS	818
GSGSYDTRALPSLPLHPMSS	819
GSGSSGVTMYPKLPPHWSMA	820
GSGSSGVRMYPKLPPHWSMA	821
GSGSSSMRMVPTIPGSAKHG	822
RNR	NR
QT	NR
RQK	NR
NRQ	NR
RQK	NR
RNRQKT	823
RNRQ	824
RNRQK	825
NRQKT	826
RQKT	827

Table 16—SH3 antagonist peptide sequences

Sequence/structure	SEQ ID NO:
RPLPPLP	828
RELPPLP	829
SPLPPLP	830
GPLPPLP	831
RPLPIPP	832
RPLPIPP	833
RRLPPTP	834
RQLPPTP	835
RPLPSRP	836
RPLPTRP	837
SRLPPLP	838
RALPSPP	839
RRLPRTP	840

RPVPPIT	841
ILAPPVP	842
RPLPMLP	843
RPLPILP	844
RPLPSLP	845
RPLPSLP	846
RPLPMIP	847
RPLPLIP	848
RPLPPTP	849
RSLPPLP	850
RPQPPPP	851
RQLPIPP	852
XXXRPLPPLPXP	853
XXXRPLPPIPXX	854
XXXRPLPPLPXX	855
RXXRPLPPLPXP	856
RXXRPLPPLPPP	857
PPPYPPPPIPXX	858
PPPYPPPPVPXX	859
LXXRPLPXΨP	860
ΨXXRPLPXLP	861
PPXΘXPPPΨP	862
+PPΨPXKPXWL	863
RPXΨPΨR+SXP	864
PPVPPRPXXTL	865
ΨPΨLPΨK	866
+ΘDXPLPXLP	867

Table 17—Somatostatin or cortistatin mimetic peptide sequences

Sequence/structure	**SEQ ID NO:**
X^1-X^2-Asn-Phe-Phe-Trp-Lys-Thr-Phe-X^3-Ser-X^4	868
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	869
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	870
Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	871
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	872
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	873

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	874
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	875
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	876
Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys	877
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	878
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	879
Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys	880
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	881
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	882
Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	883
Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	884
Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	885
Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	886
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	887
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	888
Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys	889
Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	890
Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	891
Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys	892

Table 18—UKR antagonist peptide sequences

Sequence/structure	**SEQ ID NO:**
AEPMPHSLNFSQYLWYT	893
AEHTYSSLWDTYSPLAF	894
AELDLWMRHYPLSFSNR	895
AESSLWTRYAWPSMPSY	896
AEWHPGLSFGSYLWSKT	897
AEPALLNWSFFFNPGLH	898
AEWSFYNLHLPEPQTIF	899
AEPLDLWSLYSLPPLAM	900
AEPTLWQLYQFPLRLSG	901
AEISFSELMWLRSTPAF	902
AELSEADLWTTWFGMGS	903
AESSLWRIFSPSALMMS	904
AESLPTLTSILWGKESV	905
AETLFMDLWHDKHILLT	906
AEILNFPLWHEPLWSTE	907

AESQTGTLNTLFWNTLR	908
AEPVYQYELDSYLRSYY	909
AELDLSTFYDIQYLLRT	910
AEFFKLGPNGYVYLHSA	911
FKLXXXGYVYL	912
AESTYHHLSLGYMYTLN	913
YHXLXXGYMYT	914

Table 19—Macrophage and/or T-cell inhibiting peptide sequences

Sequence/structure	SEQ ID NO:
Xaa-Yaa-Arg	NR
Arg-Yaa-Xaa	NR
Xaa-Arg-Yaa	NR
Yaa-Arg-Xaa	NR
Ala-Arg	NR
Arg-Arg	NR
Asn-Arg	NR
Asp-Arg	NR
Cys-Arg	NR
Gln-Arg	NR
Glu-Arg	NR
Gly-Arg	NR
His-arg	NR
Ile-Arg	NR
Leu-Arg	NR
Lys-Arg	NR
Met-Arg	NR
Phe-Arg	NR
Ser-Arg	NR
Thr-Arg	NR
Trp-Arg	NR
Tyr-Arg	NR
Val-Arg	NR
Ala-Glu-Arg	NR
Arg-Glu-Arg	NR

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

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

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

Table 20—Additional Exemplary Pharmacologically Active Peptides

Sequence/structure	SEQ ID NO:	Activity
VEPNCDIHVMWEWECFERL	915	VEGF-antagonist
GERWCFDGPLTWVCGEES	916	VEGF-antagonist
RGWVEICVADDNGMCVTEAQ	917	VEGF-antagonist
GWDECDVARMWEWECFAGV	918	VEGF- antagonist
GERWCFDGPRAWVCGWEI	919	VEGF- antagonist
EELWCFDGPRAWVCGYVK	920	VEGF- antagonist
RGWVEICAADDYGRCLTEAQ	921	VEGF- antagonist
RGWVEICESDVWGRCL	922	VEGF- antagonist
RGWVEICESDVWGRCL	923	VEGF- antagonist
GGNECDIARMWEWECFERL	924	VEGF- antagonist
RGWVEICAADDYGRCL	925	VEGF-antagonist
CTTHWGFTLC	926	MMP inhibitor
CLRSGXGC	927	MMP inhibitor
CXXHWGFXXC	928	MMP inhibitor

CXPXC	929	MMP inhibitor
CRRHWGFEFC	930	MMP inhibitor
STTHWGFTLS	931	MMP inhibitor
CSLHWGFWWC	932	CTLA4-mimetic
GFVCSGIFAVGVGRC	933	CTLA4-mimetic
APGVRLGCAVLGRYC	934	CTLA4-mimetic
LLGRMK	935	Antiviral (HBV)
ICVVQDWGHHRCTAGHMANLTSHASAI	936	C3b antagonist
ICVVQDWGHHRCT	937	C3b antagonist
CVVQDWGHHAC	938	C3b antagonist
STGGFDDVYDWARGVSSALTTTLVATR	939	Vinculin-binding
STGGFDDVYDWARRVSSALTTTLVATR	940	Vinculin-binding
SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	941	Vinculin-binding
SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	942	Vinculin-binding
SSPSLYTQFLVNYESAATRIQDLLIASRPSR	943	Vinculin-binding
SSTGWVDLLGALQRAADATRTSIPPSLQNSR	944	Vinculin-binding
DVYTKKELIECARRVSEK	945	Vinculin-binding
EKGSYYPGSGIAQFHIDYNNVS	946	C4BP-binding
SGIAQFHIDYNNVSSAEGWHVN	947	C4BP-binding
LVTVEKGSYYPGSGIAQFHIDYNNVSSAEGWHVN	948	C4BP-binding
SGIAQFHIDYNNVS	949	C4BP-binding
LLGRMK	950	anti-HBV
ALLGRMKG	951	anti-HBV
LDPAFR	952	anti-HBV
CXXRGDC	953	Inhibition of platelet aggregation
RPLPPLP	954	Src antagonist
PPVPPR	955	Src antagonist
XFXDXWXXLXX	956	Anti-cancer (particularly for sarcomas)
KACRRLFGPVDSEQLSRDCD	957	p16-mimetic
RERWNFDFVTETPLEGDFAW	958	p16-mimetic
KRRQTSMTDFYHSKRRLIFS	959	p16-mimetic
TSMTDFYHSKRRLIFSKRKP	960	p16-mimetic
RRLIF	961	p16-mimetic
KRRQTSATDFYHSKRRLIFSRQIKIWFQNRRMKWKK	962	p16-mimetic
KRRLIFSKRQIKIWFQNRRMKWKK	963	p16-mimetic

Asn Gln Gly Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys Phe Gln	964	CAP37 mimetic/LPS binding
Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr Ala Ala Ser Cys	965	CAP37 mimetic/LPS binding
Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val	966	CAP37 mimetic/LPS binding
WHWRHRIPLQLAAGR	967	carbohydrate (GD1 alpha) mimetic
LKTPRV	968	β2GPI Ab binding
NTLKTPRV	969	β2GPI Ab binding
NTLKTPRVGGC	970	β2GPI Ab binding
KDKATF	971	β2GPI Ab binding
KDKATFGCHD	972	β2GPI Ab binding
KDKATFGCHDGC	973	β2GPI Ab binding
TLRVYK	974	β2GPI Ab binding
ATLRVYKGG	975	β2GPI Ab binding
CATLRVYKGG	976	β2GPI Ab binding
INLKALAALAKKIL	977	Membrane-transporting
GWT	NR	Membrane-transporting
GWTLNSAGYLLG	978	Membrane-transporting
GWTLNSAGYLLGKINLKALAALAKKIL	979	Membrane-transporting
CVHAYRS	980	Antiproliferative, antiviral
CVHAYRA	981	Antiproliferative, antiviral
CVHAPRS	982	Antiproliferative, antiviral
CVHAPRA	983	Antiproliferative, antiviral
CVHSYRS	984	Antiproliferative, antiviral
CVHSYRA	985	Antiproliferative, antiviral
CVHSPRS	986	Antiproliferative, antiviral

CVHSPRA	987	Antiproliferative, antiviral
CVHTYRS	988	Antiproliferative, antiviral
CVHTYRA	989	Antiproliferative, antiviral
CVHTPRS	990	Antiproliferative, antiviral
CVHTPRA	991	Antiproliferative, antiviral
HWAWFK	992	anti-ischemic, growth hormone-liberating

TABLE 21

MYOSTATIN INHIBITOR PEPTIDES

PEPTIBODY NAME	SEQ ID	PEPTIDE SEQUENCE
Myostatin-TN8-Con1	1036	KDKCKMWHWMCKPP
Myostatin-TN8-Con2	1037	KDLCAMWHWMCKPP
Myostatin-TN8-Con3	1038	KDLCKMWKWMCKPP
Myostatin-TN8-Con4	1039	KDLCKMWHWMCKPK
Myostatin-TN8-Con5	1040	WYPCYEFHFWCYDL
Myostatin-TN8-Con6	1041	WYPCYEGHFWCYDL
Myostatin-TN8-Con7	1042	IFGCKWWDVQCYQF
Myostatin-TN8-Con8	1043	IFGCKWWDVDCYQF
Myostatin-TN8-Con9	1044	ADWCVSPNWFCMVM
Myostatin-TN8-Con10	1045	HKFCPWWALFCWDF
Myostatin-TN8-1	1046	KDLCKMWHWMCKPP
Myostatin-TN8-2	1047	IDKCAIWGWMCPPL
Myostatin-TN8-3	1048	WYPCGEFGMWCLNV
Myostatin-TN8-4	1049	WFTCLWNCDNE
Myostatin-TN8-5	1050	HTPCPWFAPLCVEW
Myostatin-TN8-6	1051	KEWCWRWKWMCKPE
Myostatin-TN8-7	1052	FETCPSWAYFCLDI
Myostatin-TN8-8	1053	AYKCEANDWGCWWL
Myostatin-TN8-9	1054	NSWCEDQWHRCWWL
Myostatin-TN8-10	1055	WSACYAGHFWCYDL
Myostatin-TN8-11	1056	ANWCVSPNWFCMVM
Myostatin-TN8-12	1057	WTECYQQEFWCWNL

Myostatin-TN8-13	1058	ENTCERWKWMCPPK
Myostatin-TN8-14	1059	WLPCHQEGFWCMNF
Myostatin-TN8-15	1060	STMCSQWHWMCNPF
Myostatin-TN8-16	1061	IFGCHWWDVDCYQF
Myostatin-TN8-17	1062	IYGCKWWDIQCYDI
Myostatin-TN8-18	1063	PDWCIDPDWWCKFW
Myostatin-TN8-19	1064	QGHCTRWPWMCPPY
Myostatin-TN8-20	1065	WQECYREGFWCLQT
Myostatin-TN8-21	1066	WFDCYGPGFKCWSP
Myostatin-TN8-22	1067	GVRCPKGHLWCLYP
Myostatin-TN8-23	1068	HWACGYWPWSCKWV
Myostatin-TN8-24	1069	GPACHSPWWWCVFG
Myostatin-TN8-25	1070	TTWCISPMWFCSQQ
Myostatin-TN8-26	1071	HKFCPPWAIFCWDF
Myostatin-TN8-27	1072	PDWCVSPRWYCNMW
Myostatin-TN8-28	1073	VWKCHWFGMDCEPT
Myostatin-TN8-29	1074	KKHCQIWTWMCAPK
Myostatin-TN8-30	1075	WFQCGSTLFWCYNL
Myostatin-TN8-31	1076	WSPCYDHYFYCYTI
Myostatin-TN8-32	1077	SWMCGFFKEVCMWV
Myostatin-TN8-33	1078	EMLCMIHPVFCNPH
Myostatin-TN8-34	1079	LKTCNLWPWMCPPL
Myostatin-TN8-35	1080	VVGCKWYEAWCYNK
Myostatin-TN8-36	1081	PIHCTQWAWMCPPT
Myostatin-TN8-37	1082	DSNCPWYFLSCVIF
Myostatin-TN8-38	1083	HIWCNLAMMKCVEM
Myostatin-TN8-39	1084	NLQCIYFLGKCIYF
Myostatin-TN8-40	1085	AWRCMWFSDVCTPG
Myostatin-TN8-41	1086	WFRCFLDADWCTSV
Myostatin-TN8-42	1087	EKICQMWSWMCAPP
Myostatin-TN8-43	1088	WFYCHLNKSECTEP
Myostatin-TN8-44	1089	FWRCAIGIDKCKRV
Myostatin-TN8-45	1090	NLGCKWYEVWCFTY
Myostatin-TN8-46	1091	IDLCNMWDGMCYPP
Myostatin-TN8-47	1092	EMPCNIWGWMCPPV
Myostatin-TN12-1	1093	WFRCVLTGIVDWSECFGL
Myostatin-TN12-2	1094	GFSCTFGLDEFYVDCSPF
Myostatin-TN12-3	1095	LPWCHDQVNADWGFCMLW

Myostatin-TN12-4	1096	YPTCSEKFWIYGQTCVLW
Myostatin-TN12-5	1097	LGPCPIHHGPWPQYCVYW
Myostatin-TN12-6	1098	PFPCETHQISWLGHCLSF
Myostatin-TN12-7	1099	HWGCEDLMWSWHPLCRRP
Myostatin-TN12-8	1100	LPLCDADMMPTIGFCVAY
Myostatin-TN12-9	1101	SHWCETTFWMNYAKCVHA
Myostatin-TN12-10	1102	LPKCTHVPFDQGGFCLWY
Myostatin-TN12-11	1103	FSSCWSPVSRQDMFCVFY
Myostatin-TN12-13	1104	SHKCEYSGWLQPLCYRP
Myostatin-TN12-14	1105	PWWCQDNYVQHMLHCDSP
Myostatin-TN12-15	1106	WFRCMLMNSFDAFQCVSY
Myostatin-TN12-16	1107	PDACRDQPWYMFMGCMLG
Myostatin-TN12-17	1108	FLACFVEFELCFDS
Myostatin-TN12-18	1109	SAYCIITESDPYVLCVPL
Myostatin-TN12-19	1110	PSICESYSTMWLPMCQHN
Myostatin-TN12-20	1111	WLDCHDDSWAWTKMCRSH
Myostatin-TN12-21	1112	YLNCVMMNTSPFVECVFN
Myostatin-TN12-22	1113	YPWCDGFMIQQGITCMFY
Myostatin-TN12-23	1114	FDYCTWLNGFKDWKCWSR
Myostatin-TN12-24	1115	LPLCNLKEISHVQACVLF
Myostatin-TN12-25	1116	SPECAFARWLGIEQCQRD
Myostatin-TN12-26	1117	YPQCFNLHLLEWTECDWF
Myostatin-TN12-27	1118	RWRCEIYDSEFLPKCWFF
Myostatin-TN12-28	1119	LVGCDNVWHRCKLF
Myostatin-TN12-29	1120	AGWCHVWGEMFGMGCSAL
Myostatin-TN12-30	1121	HHECEWMARWMSLDCVGL
Myostatin-TN12-31	1122	FPMCGIAGMKDFDFCVWY
Myostatin-TN12-32	1123	RDDCTFWPEWLWKLCERP
Myostatin-TN12-33	1124	YNFCSYLFGVSKEACQLP
Myostatin-TN12-34	1125	AHWCEQGPWRYGNICMAY
Myostatin-TN12-35	1126	NLVCGKISAWGDEACARA
Myostatin-TN12-36	1127	HNVCTIMGPSMKWFCWND
Myostatin-TN12-37	1128	NDLCAMWGWRNTIWCQNS
Myostatin-TN12-38	1129	PPFCQNDNDMLQSLCKLL
Myostatin-TN12-39	1130	WYDCNVPNELLSGLCRLF
Myostatin-TN12-40	1131	YGDCDQNHWMWPFTCLSL
Myostatin-TN12-41	1132	GWMCHFDLHDWGATCQPD
Myostatin-TN12-42	1133	YFHCMFGGHEFEVHCESF

Myostatin-TN12-43	1134	AYWCWHGQCVRF
Myostatin-Linear-1	1135	SEHWTFTDWDGNEWWVRPF
Myostatin-Linear-2	1136	MEMLDSLFELLKDMVPISKA
Myostatin-Linear-3	1137	SPPEEALMEWLGWQYGKFT
Myostatin-Linear-4	1138	SPENLLNDLYILMTKQEWYG
Myostatin-Linear-5	1139	FHWEEGIPFHVVTPYSYDRM
Myostatin-Linear-6	1140	KRLLEQFMNDLAELVSGHS
Myostatin-Linear-7	1141	DTRDALFQEFYEFVRSRLVI
Myostatin-Linear-8	1142	RMSAAPRPLTYRDIMDQYWH
Myostatin-Linear-9	1143	NDKAHFFEMFMFDVHNFVES
Myostatin-Linear-10	1144	QTQAQKIDGLWELLQSIRNQ
Myostatin-Linear-11	1145	MLSEFEEFLGNLVHRQEA
Myostatin-Linear-12	1146	YTPKMGSEWTSFWHNRIHYL
Myostatin-Linear-13	1147	LNDTLLRELKMVLNSLSDMK
Myostatin-Linear-14	1148	FDVERDLMRWLEGFMQSAAT
Myostatin-Linear-15	1149	HHGWNYLRKGSAPQWFEAWV
Myostatin-Linear-16	1150	VESLHQLQMWLDQKLASGPH
Myostatin-Linear-17	1151	RATLLKDFWQLVEGYGDN
Myostatin-Linear-18	1152	EELLREFYRFVSAFDY
Myostatin-Linear-19	1153	GLLDEFSHFIAEQFYQMPGG
Myostatin-Linear-20	1154	YREMSMLEGLLDVLERLQHY
Myostatin-Linear-21	1155	HNSSQMLLSELIMLVGSMMQ
Myostatin-Linear-22	1156	WREHFLNSDYIRDKLIAIDG
Myostatin-Linear-23	1157	QFPFYVFDDLPAQLEYWIA
Myostatin-Linear-24	1158	EFFHWLHNHRSEVNHWLDMN
Myostatin-Linear-25	1159	EALFQNFFRDVLTLSEREY
Myostatin-Linear-26	1160	QYWEQQWMTYFRENGLHVQY
Myostatin-Linear-27	1161	NQRMMLEDLWRIMTPMFGRS
Myostatin-Linear-29	1162	FLDELKAELSRHYALDDLDE
Myostatin-Linear-30	1163	GKLIEGLLNELMQLETFMPD
Myostatin-Linear-31	1164	ILLLDEYKKDWKSWF
Myostatin-2xTN8-19 kc	1165	QGHCTRWPWMCPPYGSGSATGGSGSTASSGSGSATG QGHCTRWPWMCPPY
Myostatin-2xTN8-con6	1166	WYPCYEGHFWCYDLGSGSTASSGSGSATGWYPCYEG HFWCYDL
Myostatin-2xTN8-5 kc	1167	HTPCPWFAPLCVEWGSGSATGGSGSTASSGSGSATGH TPCPWFAPLCVEW

Myostatin-2xTN8-18 kc	1168	PDWCIDPDWWCKFWGSGSATGGSGSTASSGSGSATG PDWCIDPDWWCKFW
Myostatin-2xTN8-11 kc	1169	ANWCVSPNWFCMVMGSGSATGGSGSTASSGSGSAT GANWCVSPNWFCMVM
Myostatin-2xTN8-25 kc	1170	PDWCIDPDWWCKFWGSGSATGGSGSTASSGSGSATG PDWCIDPDWWCKFW
Myostatin-2xTN8-23 kc	1171	HWACGYWPWSCKWVGSGSATGGSGSTASSGSGSAT GHWACGYWPWSCKWV
Myostatin-TN8-29-19 kc	1172	KKHCQIWTWMCAPKGSGSATGGSGSTASSGSGSATG QGHCTRWPWMCPPY
Myostatin-TN8-19-29 kc	1173	QGHCTRWPWMCPPYGSGSATGGSGSTASSGSGSATG KKHCQIWTWMCAPK
Myostatin-TN8-29-19 kn	1174	KKHCQIWTWMCAPKGSGSATGGSGSTASSGSGSATG QGHCTRWPWMCPPY
Myostatin-TN8-29-19-8g	1175	KKHCQIWTWMCAPKGGGGGGGGQGHCTRWPWMCP PY
Myostatin-TN8-19-29-6gc	1176	QGHCTRWPWMCPPYGGGGGGKKHCQIWTWMCAPK

TABLE 22

MYOSTATIN INHIBITOR PEPTIDES

Affinity- matured peptibody	**SEQ ID NO:**	**Peptide sequence**
mTN8-19-1	1177	VALHGQCTRWPWMCPPQREG
mTN8-19-2	1178	YPEQGLCTRWPWMCPPQTLA
mTN8-19-3	1179	GLNQGHCTRWPWMCPPQDSN
mTN8-19-4	1180	MITQGQCTRWPWMCPPQPSG
mTN8-19-5	1181	AGAQEHCTRWPWMCAPNDWI
mTN8-19-6	1182	GVNQGQCTRWRWMCPPNGWE
mTN8-19-7	1183	LADHGQCIRWPWMCPPEGWE
mTN8-19-8	1184	ILEQAQCTRWPWMCPPQRGG
mTN8-19-9	1185	TQTHAQCTRWPWMCPPQWEG
mTN8-19-10	1186	VVTQGHCTLWPWMCPPQRWR

mTN8-19-11	1187	IYPHDQCTRWPWMCPPQPYP
mTN8-19-12	1188	SYWQGQCTRWPWMCPPQWRG
mTN8-19-13	1189	MWQQGHCTRWPWMCPPQGWG
mTN8-19-14	1190	EFTQWHCTRWPWMCPPQRSQ
mTN8-19-15	1191	LDDQWQCTRWPWMCPPQGFS
mTN8-19-16	1192	YQTQGLCTRWPWMCPPQSQR
mTN8-19-17	1193	ESNQGQCTRWPWMCPPQGGW
mTN8-19-18	1194	WTDRGPCTRWPWMCPPQANG
mTN8-19-19	1195	VGTQGQCTRWPWMCPPYETG
mTN8-19-20	1196	PYEQGKCTRWPWMCPPYEVE
mTN8-19-21	1197	SEYQGLCTRWPWMCPPQGWK
mTN8-19-22	1198	TFSQGHCTRWPWMCPPQGWG
mTN8-19-23	1199	PGAHDHCTRWPWMCPPQSRY
mTN8-19-24	1200	VAEEWHCRRWPWMCPPQDWR
mTN8-19-25	1201	VGTQGHCTRWPWMCPPQPAG
mTN8-19-26	1202	EEDQAHCRSWPWMCPPQGWV
mTN8-19-27	1203	ADTQGHCTRWPWMCPPQHWF
mTN8-19-28	1204	SGPQGHCTRWPWMCAPQGWF
mTN8-19-29	1205	TLVQGHCTRWPWMCPPQRWV
mTN8-19-30	1206	GMAHGKCTRWAWMCPPQSWK
mTN8-19-31	1207	ELYHGQCTRWPWMCPPQSWA
mTN8-19-32	1208	VADHGHCTRWPWMCPPQGWG
mTN8-19-33	1209	PESQGHCTRWPWMCPPQGWG
mTN8-19-34	1210	IPAHGHCTRWPWMCPPQRWR
mTN8-19-35	1211	FTVHGHCTRWPWMCPPYGWV
mTN8-19-36	1212	PDFPGHCTRWRWMCPPQGWE
mTN8-19-37	1213	QLWQGPCTQWPWMCPPKGRY
mTN8-19-38	1214	HANDGHCTRWQWMCPPQWGG
mTN8-19-39	1215	ETDHGLCTRWPWMCPPYGAR
mTN8-19-40	1216	GTWQGLCTRWPWMCPPQGWQ
mTN8-19 con1	1217	VATQGQCTRWPWMCPPQGWG
mTN8-19 con2	1218	VATQGQCTRWPWMCPPQRWG
mTN8 con6-1	1219	QREWYPCYGGHLWCYDLHKA
mTN8 con6-2	1220	ISAWYSCYAGHFWCWDLKQK
mTN8 con6-3	1221	WTGWYQCYGGHLWCYDLRRK

mTN8 con6-4	1222	KTFWYPCYDGHFWCYNLKSS
mTN8 con6-5	1223	ESRWYPCYEGHLWCFDLTET

TABLE 23

MYOSTATIN INHIBITOR PEPTIDES

Affinity matured peptibody	SEQ ID NO:	Peptide Sequence
L2	1224	MEMLDSLFELLKDMVPISKA
mL2-Con1	1225	RMEMLESLLELLKEIVPMSKAG
mL2-Con2	1226	RMEMLESLLELLKEIVPMSKAR
mL2-1	1227	RMEMLESLLELLKDIVPMSKPS
mL2-2	1228	GMEMLESLFELLQEIVPMSKAP
mL2-3	1229	RMEMLESLLELLKDIVPISNPP
mL2-4	1230	RIEMLESLLELLQEIVPISKAE
mL2-5	1231	RMEMLQSLLELLKDIVPMSNAR
mL2-6	1232	RMEMLESLLELLKEIVPTSNGT
mL2-7	1233	RMEMLESLFELLKEIVPMSKAG
mL2-8	1234	RMEMLGSLLELLKEIVPMSKAR
mL2-9	1235	QMELLDSLFELLKEIVPKSQPA
mL2-10	1236	RMEMLDSLLELLKEIVPMSNAR
mL2-11	1237	RMEMLESLLELLHEIVPMSQAG
mL2-12	1238	QMEMLESLLQLLKEIVPMSKAS
mL2-13	1239	RMEMLDSLLELLKDMVPMTTGA
mL2-14	1240	RIEMLESLLELLKDMVPMANAS
mL2-15	1241	RMEMLESLLQLLNEIVPMSRAR
mL2-16	1242	RMEMLESLFDLLKELVPMSKGV
mL2-17	1243	RIEMLESLLELLKDIVPIQKAR
mL2-18	1244	RMELLESLFELLKDMVPMSDSS
mL2-19	1245	RMEMLESLLEVLQEIVPRAKGA
mL2-20	1246	RMEMLDSLLQLLNEIVPMSHAR
mL2-21	1247	RMEMLESLLELLKDIVPMSNAG

mL2-22	1248	RMEMLQSLFELLKGMVPISKAG
mL2-23	1249	RMEMLESLLELLKEIVPNSTAA
mL2-24	1250	RMEMLQSLLELLKEIVPISKAG
mL2-25	1251	RIEMLDSLLELLNELVPMSKAR
L-15	1252	HHGWNYLRKGSAPQWFEAWV
mL15-con1	1253	QVESLQQLLMWLDQKLASGPQG
mL15-1	1254	RMELLESLFELLKEMVPRSKAV
mL15-2	1255	QAVSLQHLLMWLDQKLASGPQH
mL15-3	1256	DEDSLQQLLMWLDQKLASGPQL
mL15-4	1257	PVASLQQLLIWLDQKLAQGPHA
mL15-5	1258	EVDELQQLLNWLDHKLASGPLQ
mL15-6	1259	DVESLEQLLMWLDHQLASGPHG
mL15-7	1260	QVDSLQQVLLWLEHKLALGPQV
mL15-8	1261	GDESLQHLLMWLEQKLALGPHG
mL15-9	1262	QIEMLESLLDLLRDMVPMSNAF
mL15-10	1263	EVDSLQQLLMWLDQKLASGPQA
mL15-11	1264	EDESLQQLLIYLDKMLSSGPQV
mL15-12	1265	AMDQLHQLLIWLDHKLASGPQA
mL15-13	1266	RIEMLESLLELLDEIALIPKAW
mL15-14	1267	EVVSLQHLLMWLEHKLASGPDG
mL15-15	1268	GGESLQQLLMWLDQQLASGPQR
mL15-16	1269	GVESLQQLLIFLDHMLVSGPHD
mL15-17	1270	NVESLEHLMMWLERLLASGPYA
mL15-18	1271	QVDSLQQLLIWLDHQLASGPKR
mL15-19	1272	EVESLQQLLMWLEHKLAQGPQG
mL15-20	1273	EVDSLQQLLMWLDQKLASGPHA
mL15-21	1274	EVDSLQQLLMWLDQQLASGPQK
mL15-22	1275	GVEQLPQLLMWLEQKLASGPQR
mL15-23	1276	GEDSLQQLLMWLDQQLAAGPQV
mL15-24	1277	ADDSLQQLLMWLDRKLASGPHV
mL15-25	1278	PVDSLQQLLIWLDQKLASGPQG
L-17	1279	RATLLKDFWQLVEGYGDN
mL17-con1	1280	DWRATLLKEFWQLVEGLGDNLV
mL17-con2	1281	QSRATLLKEFWQLVEGLGDKQA
mL17-1	1282	DGRATLLTEFWQLVQGLGQKEA

mL17-2	1283	LARATLLKEFWQLVEGLGEKVV
mL17-3	1284	GSRDTLLKEFWQLVVGLGDMQT
mL17-4	1285	DARATLLKEFWQLVDAYGDRMV
mL17-5	1286	NDRAQLLRDFWQLVDGLGVKSW
mL17-6	1287	GVRETLLYELWYLLKGLGANQG
mL17-7	1288	QARATLLKEFCQLVGCQGDKLS
mL17-8	1289	QERATLLKEFWQLVAGLGQNMR
mL17-9	1290	SGRATLLKEFWQLVQGLGEYRW
mL17-10	1291	TMRATLLKEFWLFVDGQREMQW
mL17-11	1292	GERATLLNDFWQLVDGQGDNTG
mL17-12	1293	DERETLLKEFWQLVHGWGDNVA
mL17-13	1294	GGRATLLKELWQLLEGQGANLV
mL17-14	1295	TARATLLNELVQLVKGYGDKLV
mL17-15	1295	GMRATLLQEFWQLVGGQGDNWM
mL17-16	1297	STRATLLNDLWQLMKGWAEDRG
mL17-17	1298	SERATLLKELWQLVGGWGDNFG
mL17-18	1299	VGRATLLKEFWQLVEGLVGQSR
mL17-19	1300	EIRATLLKEFWQLVDEWREQPN
mL17-20	1301	QLRATLLKEFLQLVHGLGETDS
mL17-21	1302	TQRATLLKEFWQLIEGLGGKHV
mL17-22	1303	HYRATLLKEFWQLVDGLREQGV
mL17-23	1304	QSRVTLLREFWQLVESYRPIVN
mL17-24	1305	LSRATLLNEFWQFVDGQRDKRM
mL17-25	1306	WDRATLLNDFWHLMEELSQKPG
mL17-26	1307	QERATLLKEFWRMVEGLGKNRG
mL17-27	1308	NERATLLREFWQLVGGYGVNQR
L-20	1309	YREMSMLEGLLDVLERLQHY
mL20-1	1310	HQRDMSMLWELLDVLDGLRQYS
mL20-2	1311	TQRDMSMLDGLLEVLDQLRQQR
mL20-3	1312	TSRDMSLLWELLEELDRLGHQR
mL20-4	1313	MQHDMSMLYGLVELLESLGHQI
mL20-5	1314	WNRDMRMLESLFEVLDGLRQQV
mL20-6	1315	GYRDMSMLEGLLAVLDRLGPQL
mL20 con1	1316	TQRDMSMLEGLLEVLDRLGQQR

mL20 con2	1317	WYRDMSMLEGLLEVLDRLGQQR
L-21	1318	HNSSQMLLSELIMLVGSMMQ
mL21-1	1319	TQNSRQMLLSDFMMLVGSMIQG
mL21-2	1320	MQTSRHILLSEFMMLVGSIMHG
mL21-3	1321	HDNSRQMLLSDLLHLVGTMIQG
mL21-4	1322	MENSRQNLLRELIMLVGNMSHQ
mL21-5	1323	QDTSRHMLLREFMMLVGEMIQG
mL21 con1	1324	DQNSRQMLLSDLMILVGSMIQG
L-24	1325	EFFHWLHNHRSEVNHWLDMN
mL24-1	1326	NVFFQWVQKHGRVVYQWLDINV
mL24-2	1327	FDFLQWLQNHRSEVEHWLVMDV

TABLE 24

MYOSTATIN INHIBITOR PEPTIDES

Peptibody Name	Peptide
2x mTN8–Con6–(N)–1K	M–GAQ–WYPCYEGHFWCYDL–GSGSATGGSGSTASSGSGSATG–WYPCYEGHFWCYDL–LE–5G–FC (SEQ ID NO: 1328)
2x mTN8–Con6–(C)–1K	FC–5G–AQ–WYPCYEGHFWCYDL–GSGSATGGSGSTASSGSGSATG– WYPCYEGHFWCYDL–LE (SEQ ID NO: 1329)
2x mTN8–Con7–(N)–1K	M–GAQ–IFGCKWWDVQCYQF–GSGSATGGSGSTASSGSGSATG–IFGCKWWDVQCYQF–LE–5G–FC (SEQ ID NO: 1330)
2x mTN8–Con7–(C)–1K	FC–5G–AQ–IFGCKWWDVQCYQF–GSGSATGGSGSTASSGSGSATG–IFGCKWWDVQCYQF–LE (SEQ ID NO: 1331)

2x mTN8–Con8–(N)–1K	M–GAQ–IFGCKWWDVDCYQF–GSGSATGGSGSTASSGSGSATG–IFGCKWWDVDCYQF–LE–5G–FC (SEQ ID NO: 1332)
2x mTN8–Con8–(C)–1K	FC–5G–AQ–IFGCKWWDVDCYQF–GSGSATGGSGSTASSGSGSATG– IFGCKWWDVDCYQF–LE (SEQ ID NO: 1333)
2X mTN8–19–7	FC–5G–AQ–LADHGQCIRWPWMCPPEGWELEGSGSATGGSGSTASSGSGSATGLADHGQCIRWPWMCPPEGWE–LE (SEQ ID NO: 1334)
2X mTN8–19–7 ST—GG del2x LE	FC–5G–AQ–LADHGQCIRWPWMCPPEGWEGSGSATGGSGGGASSGSGSATGLADHGQCIRWPWMCPPEGWE (SEQ ID NO: 1335)
2X mTN8–19–21	FC–5G–AQ–SEYQGLCTRWPWMCPPQGWKLEGSGSATGGSGSTASSGSGSATGSEYQGLCTRWPWMCPPQGWK –LE (SEQ ID NO: 1336)
2X mTN8–19–21 ST—GG del2x LE	FC–5G–AQ–SEYQGLCTRWPWMCPPQGWKGSGSATGGSGGGASSGSGSATGSEYQGLCTRWPWMCPPQGWK (SEQ ID NO: 1337)

2X mTN8–19–22	FC–5G–AQ–TFSQGHCTRWPWMCPPQGWGLEGSGSATGGSGSTASSGSGSATGTFSQGHCTRWPWMCPPQGWG –L E (SEQ ID NO: 1338)
2X mTN8–19–32	FC–5G–AQ–VADHGHCTRWPWMCPPQGWGLEGSGSATGGSGSTASSGSGSATGVADHGHCTRWPWMCPPQGWG–LE (SEQ ID NO: 1339)
2X mTN8–19–32 ST—GG del2x LE	FC–5G–AQ–VADHGHCTRWPWMCPPQGWGGSGSATGGSGGGASSGSGSATGVADHGHCTRWPWVCPPQGWG (SEQ ID NO: 1340)
2X mTN8–19–33	FC–5G–AQ–PESQGHCTRWPWMCPPQGWGLEGSGSATGGSGSTASSGSGSATGPESQGHCTRWPWMCPPQGWGLE (SEQ ID NO: 1341)
2X mTN8–19–33 ST—GG del2x LE	FC–5G–AQ–PESQGHCTRWPWMCPPQGWGGSGSATGGSGGGASSGSGSATGPESQGHCTRWPWMCP PQGWG (SEQ ID NO: 1342)

Table 25

Integrin-antagonist peptide sequences

Sequence/structure	SEQ. ID NO:
CLCRGDCIC	1344
CWDDGWLC	1345
CWDDLWWLC	1346
CWDDGLMC	1347
CWDDGWMC	1348
CSWDDGWLC	1349
CPDDLWWLC	1350
NGR	1351
GSL	1352
RGD	1353
CGRECPRLCQSSC	1354
CNGRCVSGCAGRC	1355
CLSGSLSC	1356
GSL	1357
NGRAHA	1358
CNGRC	1359
CDCRGDCFC	1360
CGSLVRC	1361
DLXXL	1362
RTDLDSLRTYTL	1363
RTDLDSLRTY	1364
RTDLDSLRT	1365
RTDLDSLR	1366
GDLDLLKLRLTL	1367
GDLHSLRQLLSR	1368
RDDLHMLRLQLW	1369
SSDLHALKKRYG	1370
RGDLKQLSELTW	1371
CXXRGDC	1372
STGGFDDVYDWARGVSSALTTTLVATR	1373
STGGFDDVYDWARRVSSALTTTLVATR	1374
SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	1375

SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	1376
SSPSLYTQFLVNYESAATRIQDLLIASRPSR	1377
SSTGWVDLLGALQRAADATRTSIPPSLQNSR	1378
DVYTKKELIECARRVSEK	1379
RGDGX	1380
CRGDGXC	1381
CARRLDAPC	1382
CPSRLDSPC	1383
CDCRGDCFC	1384
CDCRGDCLC	1385
RGDLAALSAPPV	1386

Table 26

Selectin antagonist peptide sequences

Sequence/structure	**SEQ ID NO:**
DITWDQLWDLMK	1387
DITWDELWKIMN	1388
DYTWFELWDMMQ	1389
QITWAQLWNMMK	1390
DMTWHDLWTLMS	1391
DYSWHDLWEMMS	1392
EITWDQLWEVMN	1393
HVSWEQLWDIMN	1394
HITWDQLWRIMT	1395
RNMSWLELWEHMK	1396
AEWTWDQLWHVMNPAESQ	1397
HRAEWLALWEQMSP	1398
KKEDWLALWRIMSV	1399
ITWDQLWDLMK	1400
DITWDQLWDLMK	1401
DITWDQLWDLMK	1402
DITWDQLWDLMK	1403
CQNRYTDLVAIQNKNE	1404
AENWADNEPNNKRNNED	1405
RKNNKTWTWVGTKKALTNE	1406
KKALTNEAENWAD	1407

CQXRYTDLVAIQNKXE	1408
AENWADGEPNNKXNXED	1409

Table 27

Vinculin binding peptides

Sequence/structure	SEQ ID NO:
SSQNWDMEAGVEDLTAAMLGLLSTIHSSSR	1410
SSPSLYTQFLVNYESAATRIQDLLIASRPSR	1411
SSTGWVDLLGALQRAADATRTSIPPSLQNSR	1412
DVYTKKELIECARRVSEK	1413
STGGFDDVYDWARGVSSALTTTLVATR	1414
STGGFDDVYDWARRVSSALTTTLVATR	1415
SRGVNFSEWLYDMSAAMKEASNVFPSRRSR	1416

Table 28

Laminin-related peptide sequences

Sequence/structure	SEQ ID NO:
YIGSRYIGSR [i.e., $(YIGSR)_2$]	1417
YIGSRYIGSRYIGSR [i.e., $(YIGSR)_3$]	1418
YIGSRYIGSRYIGSRYIGSR [i.e., $(YIGSR)_4$]	1419
YIGSRYIGSRYIGSRYIGSRYIGSR [i.e., $(YIGSR)_5$]	1420
IPCNNKGAHSVGLMWWMLAR	1421
YIGSRREDVEILDVPDSGR	1422
RGDRGDYIGSRRGD	1423
YIGSRYIGSRYIGSRYIGSRYIGSR	1424
REDVEILDVYIGSRPDSGR	1425
YIGSRREDVEILDVPDSGR	1426

Table 29

NGF Modulating Peptides

SEQ ID NO:	Sequence of Peptide Portion of Fc-Peptide Fusion Product
1427	TGYTEYTEEWPMGFGYQWSF
1428	TDWLSDFPFYEQYFGLMPPG

1429	FMRFPNPWKLVEPPQGWYYG
1430	VVKAPHFEFLAPPHFHEFPF
1431	FSYIWIDETPSNIDRYMLWL
1432	VNFPKVPEDVEPWPWSLKLY
1433	TWHPKTYEEFALPFFVPEAP
1434	WHFGTPYIQQQPGVYWLQAP
1435	VWNYGPFFMNFPDSTYFLHE
1436	WRIHSKPLDYSHVWFFPADF
1437	FWDGNQPPDILVDWPWNPPV
1438	FYSLEWLKDHSEFFQTVTEW
1439	QFMELLKFFNSPGDSSHHFL
1440	TNVDWISNNWEHMKSFFTED
1441	PNEKPYQMQSWFPPDWPVPY
1442	WSHTEWVPQVWWKPPNHFYV
1443	WGEWINDAQVHMHEGFISES
1444	VPWEHDHDLWEIISQDWHIA
1445	VLHLQDPRGWSNFPPGVLEL
1446	IHGCWFTEEGCVWQ
1447	YMQCQFARDGCPQW
1448	KLQCQYSESGCPTI
1449	FLQCEISGGACPAP
1450	KLQCEFSTSGCPDL
1451	KLQCEFSTQGCPDL
1452	KLQCEFSTSGCPWL
1453	IQGCWFTEEGCPWQ
1454	SFDCDNPWGHVLQSCFGF
1455	SFDCDNPWGHKLQSCFGF

Table 30

TALL MODULATING PEPTIDES

Sequence/structure	SEQ ID NO:
LPGCKWDLLIKQWVCDPL-Λ-V^1	1456
V^1- Λ - LPGCKWDLLIKQWVCDPL	1457
LPGCKWDLLIKQWVCDPL - Λ - LPGCKWDLLIKQWVCDPL - Λ -V^1	1458
V^1- Λ - LPGCKWDLLIKQWVCDPL - Λ - LPGCKWDLLIKQWVCDPL	1459

SADCYFDILTKSDVCTSS- Λ -V^1	1460
V^1- Λ - SADCYFDILTKSDVCTSS	1461
SADCYFDILTKSDVTSS- Λ - SADCYFDILTKSDVTSS - Λ -V^1	1462
V^1- Λ - SADCYFDILTKSDVTSS - Λ - SADCYFDILTKSDVTSS	1463
FHDCKWDLLTKQWVCHGL- Λ -V^1	1464
V^1- Λ - FHDCKWDLLTKQWVCHGL	1465
FHDCKWDLLTKQWVCHGL - Λ - FHDCKWDLLTKQWVCHGL - Λ -V^1	1466
V^1- Λ - FHDCKWDLLTKQWVCHGL - Λ - FHDCKWDLLTKQWVCHGL	1467

Table 31

TALL-1 inhibitory peptibodies.

Peptibody	Peptibody SEQ ID NO	Peptide Sequence
TALL-1-8-1-a	1468	MPGTCFPFPW ECTHAGGGGG VDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK
TALL-1-8-2-a	1469	MWGACWPFPW ECFKEGGGGG VDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK
TALL-1-8-4-a	1470	MVPFCDLLTK HCFEAGGGGG VDKTHTCPPC PAPELLGGPS VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSRDELT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK

		SLSLSPGK
TALL-1-12-4-a	1471	MGSRCKYKWD VLTKQCFHHG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-3-a	1472	MLPGCKWDLL IKQWVCDPLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-5-a	1473	MSADCYFDIL TKSDVCTSSG GGGG VDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-8-a	1474	MSDDCMYDQL TRMFICSNLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-9-a	1475	MDLNCKYDEL TYKEWCQFNG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-10-a	1476	MFHDCKYDLL TRQMVCHGLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR

		DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-11-a	1477	MRNHCFWDHL LKQDICPSPG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-12-14-a	1478	MANQCWWDSL TKKNVCEFFG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1-consensus	1479	MFHDCKWDLL TKQWVCHGLG GGGGVDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK
TALL-1 12-3 tandem dimer	1480	MLPGCKWDLL IKQWVCDPLG SGSATGGSGS TASSGSGSAT HMLPGCKWDL LIKQWVCDPL GGGGGVDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK
TALL-1 consensus tandem dimer	1481	MFHDCKWDLL TKQWVCHGLG SGSATGGSGS TASSGSGSAT HMFHDCKWDL LTKQWVCHGL GGGGGVDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK

TABLE 32

ANG-2 INHIBITOR PEPTIDES

PEPTIDE	SEQ ID NO.	PEPTIDE SEQUENCE
Con4-44	1482	PIRQEECDWDPWTCEHMWEV
Con4-40	1483	TNIQEECEWDPWTCDHMPGK
Con4-4	1484	WYEQDACEWDPWTCEHMAEV
Con4-31	1485	NRLQEVCEWDPWTCEHMENV
Con4-C5	1486	AATQEECEWDPWTCEHMPRS
Con4-42	1487	LRHQEGCEWDPWTCEHMFDW
Con4-35	1488	VPRQKDCEWDPWTCEHMYVG
Con4-43	1489	SISHEECEWDPWTCEHMQVG
Con4-49	1490	WAAQEECEWDPWTCEHMGRM
Con4-27	1491	TWPQDKCEWDPWTCEHMGST
Con4-48	1492	GHSQEECGWDPWTCEHMGTS
Con4-46	1493	QHWQEECEWDPWTCDHMPSK
Con4-41	1494	NVRQEKCEWDPWTCEHMPVR
Con4-36	1495	KSGQVECNWDPWTCEHMPRN
Con4-34	1496	VKTQEHCDWDPWTCEHMREW
Con4-28	1497	AWGQEGCDWDPWTCEHMLPM
Con4-39	1498	PVNQEDCEWDPWTCEHMPPM
Con4-25	1499	RAPQEDCEWDPWTCAHMDIK
Con4-50	1500	HGQNMECEWDPWTCEHMFRY
Con4-38	1501	PRLQEECVWDPWTCEHMPLR
Con4-29	1502	RTTQEKCEWDPWTCEHMESQ
Con4-47	1503	QTSQEDCVWDPWTCDHMVSS
Con4-20	1504	QVIGRPCEWDPWTCEHLEGL
Con4-45	1505	WAQQEECAWDPWTCDHMVGL
Con4-37	1506	LPGQEDCEWDPWTCEHMVRS
Con4-33	1507	PMNQVECDWDPWTCEHMPRS
AC2-Con4	1508	FGWSHGCEWDPWTCEHMGST
Con4-32	1509	KSTQDDCDWDPWTCEHMVGP
Con4-17	1510	GPRISTCQWDPWTCEHMDQL
Con4-8	1511	STIGDMCEWDPWTCAHMQVD
AC4-Con4	1512	VLGGQGCEWDPWTCRLLQGW

Con4-1	1513	VLGGQGCQWDPWTCSHLEDG
Con4-C1	1514	TTIGSMCEWDPWTCAHMQGG
Con4-21	1515	TKGKSVCQWDPWTCSHMQSG
Con4-C2	1516	TTIGSMCQWDPWTCAHMQGG
Con4-18	1517	WVNEVVCEWDPWTCNHWDTP
Con4-19	1518	VVQVGMCQWDPWTCKHMRLQ
Con4-16	1519	AVGSQTCEWDPWTCAHLVEV
Con4-11	1520	QGMKMFCEWDPWTCAHIVYR
Con4-C4	1521	TTIGSMCQWDPWTCEHMQGG
Con4-23	1522	TSQRVGCEWDPWTCQHLTYT
Con4-15	1523	QWSWPPCEWDPWTCQTVWPS
Con4-9	1524	GTSPSFCQWDPWTCSHMVQG
TN8-Con4*	1525	QEECEWDPWTCEHM

TABLE 33

ANG-2 INHIBITOR PEPTIDES

Peptide	SEQ ID NO.	Peptide Sequence
L1-1	1526	QNYKPLDELDATLYEHFIFHYT
L1-2	1527	LNFTPLDELEQTLYEQWTLQQS
L1-3	1528	TKFNPLDELEQTLYEQWTLQHQ
L1-4	1529	VKFKPLDALEQTLYEHWMFQQA
L1-5	1530	VKYKPLDELDEILYEQQTFQER
L1-7	1531	TNFMPMDDLEQRLYEQFILQQG
L1-9	1532	SKFKPLDELEQTLYEQWTLQHA
L1-10	1533	QKFQPLDELEQTLYEQFMLQQA
L1-11	1534	QNFKPMDELEDTLYKQFLFQHS
L1-12	1535	YKFTPLDDLEQTLYEQWTLQHV
L1-13	1536	QEYEPLDELDETLYNQWMFHQR
L1-14	1537	SNFMPLDELEQTLYEQFMLQHQ
L1-15	1538	QKYQPLDELDKTLYDQFMLQQG
L1-16	1539	QKFQPLDELEETLYKQWTLQQR
L1-17	1540	VKYKPLDELDEWLYHQFTLHHQ
L1-18	1541	QKFMPLDELDEILYEQFMFQQS

L1-19	1542	QTFQPLDDLEEYLYEQWIRRYH
L1-20	1543	EDYMPLDALDAQLYEQFILLHG
L1-21	1544	HTFQPLDELEETLYYQWLYDQL
L1-22	1545	YKFNPMDELEQTLYEEFLFQHA
AC6-L1	1546	TNYKPLDELDATLYEHWILQHS
L1-C1	1547	QKFKPLDELEQTLYEQWTLQQR
L1-C2	1548	TKFQPLDELDQTLYEQWTLQQR
L1-C3	1549	TNFQPLDELDQTLYEQWTLQQR
L1	1550	KFNPLDELEETLYEQFTFQQ

TABLE 34

ANG-2 INHIBITOR PEPTIDES

Peptide	SEQ ID NO.	Sequence
Con1-1	1551	AGGMRPYDGMLGWPNYDVQA
Con1-2	1552	QTWDDPCMHILGPVTWRRCI
Con1-3	1553	APGQRPYDGMLGWPTYQRIV
Con1-4	1554	SGQLRPCEEIFGCGTQNLAL
Con1-5	1555	FGDKRPLECMFGGPIQLCPR
Con1-6	1556	GQDLRPCEDMFGCGTKDWYG
Con1	1557	KRPCEEIFGGCTYQ

TABLE 35

ANG-2 INHIBITOR PEPTIDES

Peptide	SEQ ID NO:	Sequence
12-9-1	1558	GFEYCDGMEDPFTFGCDKQT
12-9-2	1559	KLEYCDGMEDPFTQGCDNQS
12-9-3	1560	LQEWCEGVEDPFTFGCEKQR
12-9-4	1561	AQDYCEGMEDPFTFGCEMQK
12-9-5	1562	LLDYCEGVQDPFTFGCENLD
12-9-6	1563	HQEYCEGMEDPFTFGCEYQG
12-9-7	1564	MLDYCEGMDDPFTFGCDKQM
12-9-C2	1565	LQDYCEGVEDPFTFGCENQR

12-9-C1	1566	LQDYCEGVEDPFTFGCEKQR
12-9	1567	FDYCEGVEDPFTFGCDNH

Table 36

Ang-2 Binding Peptides

Peptide	Seq Id No.	Sequence
TN8-8	1568	KRPCEEMWGGCNYD
TN8-14	1569	HQICKWDPWTCKHW
TN8-Con1	1570	KRPCEEIFGGCTYQ
TN8-Con4	1571	QEECEWDPWTCEHM
TN12-9	1572	FDYCEGVEDPFTFGCDNH
L1	1573	KFNPLDELEETLYEQFTFQQ
C17	1574	QYGCDGFLYGCMIN

Table 37

Ang-2 Binding Peptides

Peptibody	Peptibody Sequence
L1 (N)	MGAQKFNPLDELEETLYEQFTFQQLEGGGGG-Fc (SEQ ID NO:1575)
L1 (N) WT	MKFNPLDELEETLYEQFTFQQLEGGGGG-Fc (SEQ ID NO:1576)
L1 (N) 1K WT	MKFNPLDELEETLYEQFTFQQGSGSATGGSGSTASSGSGSATHLEGGGGG-Fc (SEQ ID NO:1577)
2xL1 (N)	MGAQKFNPLDELEETLYEQFTFQQGGGGGGGGGKFNPLDELEETLYEQFTFQQLEGGGGG-Fc (SEQ ID NO:1578)
2xL1 (N) WT	MKFNPLDELEETLYEQFTFQQGGGGGGGGKFNPLDELEETLYEQFTFQQLEGGGGG-Fc (SEQ ID NO:1579)
Con4 (N)	MGAQQEECEWDPWTCEHMLEGGGGG-Fc (SEQ ID NO:1580)
Con4 (N) 1K-WT	MQEECEWDPWTCEHMGSGSATGGSGSTASSGSGSATHLEGGGGG-Fc (SEQ ID NO:1581)

2xCon4 (N) 1K	MGAQQEECEWDPWTCEHMGSGSATGGSGSTASSGSGSATH QEECEWDPWTCEHMLEGGGGG-Fc (SEQ ID NO:1582)
L1 (C)	M-Fc-GGGGGAQKFNPLDELEETLYEQFTFQQLE (SEQ ID NO:1583)
L1 (C) 1K	M-Fc-GGGGGAQGSGSATGGSGSTASSGSGSATHKFNPLDELEETLY EQFTFQQLE (SEQ ID NO:1584)
2xL1 (C)	M-Fc-GGGGGAQKFNPLDELEETLYEQFTFQQGGGGGGGGGKFNPLD ELEETLYEQFTFQQLE (SEQ ID NO:1585)
Con4 (C)	M-Fc-GGGGGAQQEECEWDPWTCEHMLE (SEQ ID NO:1586)
Con4 (C) 1K	M-Fc-GGGGGAQGSGSATGGSGSTASSGSGSATHQEECEWDPWTCE HMLE (SEQ ID NO:1587)
2xCon4 (C) 1K	M-Fc-GGGGGAQQEECEWDPWTCEHMGSGSATGGSGSTASSGSGS ATHQEECEWDPWTCEHMLE (SEQ ID NO:1588)
Con4-L1 (N)	MGAQEECEWDPWTCEHMGGGGGGGGKFNPLDELEETLYEQ FTFQQGSGSATGGSGSTASSGSGSATHLEGGGGG-Fc (SEQ ID NO:1589)
Con4-L1 (C)	M-Fc-GGGGGAQGSGSATGGSGSTASSGSGSATHKFNPLDELEETLY EQFTFQQGGGGGGQEECEWDPWTCEHMLE (SEQ ID NO:1590)
TN-12-9 (N)	MGAQ-FDYCEGVEDPFTFGCDNHLE-GGGGG-Fc (SEQ ID NO:1591)
C17 (N)	MGAQ-QYGCDGFLYGCMINLE-GGGGG-Fc (SEQ ID NO:1592)
TN8-8 (N)	MGAQ-KRPCEEMWGGCNYDLEGGGGG-Fc (SEQ ID NO:1593)
TN8-14 (N)	MGAQ-HQICKWDPWTCKHWLEGGGGG-Fc (SEQ ID NO:1594)
Con1 (N)	MGAQ-KRPCEEIFGGCTYQLEGGGGG-Fc (SEQ ID NO:1595)

Table 38

Ang-2 Binding Peptides

Con4 Derived Affinity-Matured Pbs	Peptibody Sequence (Seq Id No:)
Con4-44 (C)	M-Fc-GGGGGAQ-PIRQEECDWDPWTCEHMWEV-LE (SEQ ID NO: 1596)
Con4-40 (C)	M-Fc-GGGGGAQ-TNIQEECEWDPWTCDHMPGK-LE (SEQ ID NO: 1597)
Con4-4 (C)	M-Fc-GGGGGAQ-WYEQDACEWDPWTCEHMAEV-LE (SEQ ID NO: 1598)
Con4-31 (C)	M-Fc-GGGGGAQ-NRLQEVCEWDPWTCEHMENV-LE (SEQ ID NO: 1599)
Con4-C5 (C)	M-Fc-GGGGGAQ-AATQEECEWDPWTCEHMPRS-LE (SEQ ID NO: 1600)
Con4-42 (C)	M-Fc-GGGGGAQ-LRHQEGCEWDPWTCEHMFDW-LE (SEQ ID NO: 1602)
Con4-35 (C)	M-Fc-GGGGGAQ-VPRQKDCEWDPWTCEHMYVG-LE (SEQ ID NO: 1602)
Con4-43 (C)	M-Fc-GGGGGAQ-SISHEECEWDPWTCEHMQVG-LE (SEQ ID NO: 1603)
Con4-49 (C)	M-Fc-GGGGGAQ-WAAQEECEWDPWTCEHMGRM-LE (SEQ ID NO: 1604)
Con4-27 (C)	M-Fc-GGGGGAQ-TWPQDKCEWDPWTCEHMGST-LE (SEQ ID NO: 1605)
Con4-48 (C)	M-Fc-GGGGGAQ-GHSQEECGWDPWTCEHMGTS-LE (SEQ ID NO: 1606)
Con4-46 (C)	M-Fc-GGGGGAQ-QHWQEECEWDPWTCDHMPSK-LE (SEQ ID NO: 1607)
Con4-41 (C)	M-Fc-GGGGGAQ-NVRQEKCEWDPWTCEHMPVR-LE (SEQ ID NO: 1608)
Con4-36 (C)	M-Fc-GGGGGAQ-KSGQVECNWDPWTCEHMPRN-LE (SEQ ID NO: 1609)
Con4-34 (C)	M-Fc-GGGGGAQ-VKTQEHCDWDPWTCEHMREW-LE (SEQ ID NO: 1610)
Con4-28 (C)	M-Fc-GGGGGAQ-AWGQEGCDWDPWTCEHMLPM-LE

	(SEQ ID NO: 1611)
Con4-39 (C)	M-Fc-GGGGGAQ-PVNQEDCEWDPWTCEHMPPM-LE (SEQ ID NO: 1612)
Con4-25 (C)	M-Fc-GGGGGAQ-RAPQEDCEWDPWTCAHMDIK-LE (SEQ ID NO: 1613)
Con4-50 (C)	M-Fc-GGGGGAQ-HGQNMECEWDPWTCEHMFRY-LE (SEQ ID NO: 1614)
Con4-38 (C)	M-Fc-GGGGGAQ-PRLQEECVWDPWTCEHMPLR-LE (SEQ ID NO: 1615)
Con4-29 (C)	M-Fc-GGGGGAQ-RTTQEKCEWDPWTCEHMESQ-LE (SEQ ID NO: 1616)
Con4-47 (C)	M-Fc-GGGGGAQ-QTSQEDCVWDPWTCDHMVSS-LE (SEQ ID NO: 1617)
Con4-20 (C)	M-Fc-GGGGGAQ-QVIGRPCEWDPWTCEHLEGL-LE (SEQ ID NO: 1618)
Con4-45 (C)	M-Fc-GGGGGAQ-WAQQEECAWDPWTCDHMVGL-LE (SEQ ID NO: 1619)
Con4-37 (C)	M-Fc-GGGGGAQ-LPGQEDCEWDPWTCEHMVRS-LE (SEQ ID NO: 1620)
Con4-33 (C)	M-Fc-GGGGGAQ-PMNQVECDWDPWTCEHMPRS-LE (SEQ ID NO: 1621)
AC2-Con4 (C)	M-Fc-GGGGGAQ-FGWSHGCEWDPWTCEHMGST-LE (SEQ ID NO: 1622)
Con4-32 (C)	M-Fc-GGGGGAQ-KSTQDDCDWDPWTCEHMVGP-LE (SEQ ID NO: 1623)
Con4-17 (C)	M-Fc-GGGGGAQ-GPRISTCQWDPWTCEHMDQL-LE (SEQ ID NO: 1624)
Con4-8 (C)	M-Fc-GGGGGAQ-STIGDMCEWDPWTCAHMQVD-LE (SEQ ID NO: 1625)
AC4-Con4 (C)	M-Fc-GGGGGAQ-VLGGQGCEWDPWTCRLLQGW-LE (SEQ ID NO: 1626)
Con4-1 (C)	M-Fc-GGGGGAQ-VLGGQGCQWDPWTCSHLEDG-LE (SEQ ID NO: 1627)
Con4-C1 (C)	M-Fc-GGGGGAQ-TTIGSMCEWDPWTCAHMQGG-LE (SEQ ID NO: 1628)
Con4-21 (C)	M-Fc-GGGGGAQ-TKGKSVCQWDPWTCSHMQSG-LE (SEQ ID NO: 1629)
Con4-C2 (C)	M-Fc-GGGGGAQ-TTIGSMCQWDPWTCAHMQGG-LE

	(SEQ ID NO: 1630)
Con4-18 (C)	M-Fc-GGGGGAQ-WVNEVVCEWDPWTCNHWDTP-LE (SEQ ID NO: 1631)
Con4-19 (C)	M-Fc-GGGGGAQ-VVQVGMCQWDPWTCKHMRLQ-LE (SEQ ID NO: 1632)
Con4-16 (C)	M-Fc-GGGGGAQ-AVGSQTCEWDPWTCAHLVEV-LE (SEQ ID NO: 1633)
Con4-11 (C)	M-Fc-GGGGGAQ-QGMKMFCEWDPWTCAHIVYR-LE (SEQ ID NO: 1634)
Con4-C4 (C)	M-Fc-GGGGGAQ-TTIGSMCQWDPWTCEHMQGG-LE (SEQ ID NO: 1635)
Con4-23 (C)	M-Fc-GGGGGAQ-TSQRVGCEWDPWTCQHLTYT-LE (SEQ ID NO: 1636)
Con4-15 (C)	M-Fc-GGGGGAQ-QWSWPPCEWDPWTCQTVWPS-LE (SEQ ID NO: 1637)
Con4-9 (C)	M-Fc-GGGGGAQ-GTSPSFCQWDPWTCSHMVQG-LE (SEQ ID NO: 1638)
Con4-10 (C)	M-Fc-GGGGGAQ-TQGLHQCEWDPWTCKVLWPS-LE (SEQ ID NO: 1639)
Con4-22 (C)	M-Fc-GGGGGAQ-VWRSQVCQWDPWTCNLGGDW-LE (SEQ ID NO: 1640)
Con4-3 (C)	M-Fc-GGGGGAQ-DKILEECQWDPWTCQFFYGA-LE (SEQ ID NO: 1641)
Con4-5 (C)	M-Fc-GGGGGAQ-ATFARQCQWDPWTCALGGNW-LE (SEQ ID NO: 1642)
Con4-30 (C)	M-Fc-GGGGGAQ-GPAQEECEWDPWTCEPLPLM-LE (SEQ ID NO: 1643)
Con4-26 (C)	M-Fc-GGGGGAQ-RPEDMCSQWDPWTWHLQGYC-LE (SEQ ID NO: 1644)
Con4-7 (C)	M-Fc-GGGGGAQ-LWQLAVCQWDPQTCDHMGAL-LE (SEQ ID NO: 1645)
Con4-12 (C)	M-Fc-GGGGGAQ-TQLVSLCEWDPWTCRLLDGW-LE (SEQ ID NO: 1646)
Con4-13 (C)	M-Fc-GGGGGAQ-MGGAGRCEWDPWTCQLLQGW-LE (SEQ ID NO: 1647)
Con4-14 (C)	M-Fc-GGGGGAQ-MFLPNECQWDPWTCSNLPEA-LE (SEQ ID NO: 1648)
Con4-2 (C)	M-Fc-GGGGGAQ-FGWSHGCEWDPWTCRLLQGW-LE

	(SEQ ID NO: 1649)
Con4-6 (C)	M-Fc-GGGGGAQ-WPQTEGCQWDPWTCRLLHGW-LE (SEQ ID NO: 1650)
Con4-24 (C)	M-Fc-GGGGGAQ-PDTRQGCQWDPWTCRLYGMW-LE (SEQ ID NO: 1651)
AC1-Con4 (C)	M-Fc-GGGGGAQ-TWPQDKCEWDPWTCRLLQGW-LE (SEQ ID NO: 1652)
AC3-Con4 (C)	M-Fc-GGGGGAQ-DKILEECEWDPWTCRLLQGW-LE (SEQ ID NO: 1653)
AC5-Con4 (C)	M-Fc-GGGGGAQ-AATQEECEWDPWTCRLLQGW-LE (SEQ ID NO: 1654)
L1 Derived Affinity-Matured Pbs	**Peptibody Sequence (Seq Id No:)**
L1-7 (N)	MGAQ-TNFMPMDDLEQRLYEQFILQQG-LEGGGGG-Fc (SEQ ID NO: 1655)
AC6-L1 (N)	MGAQ-TNYKPLDELDATLYEHWILQHS LEGGGGG-Fc (SEQ ID NO: 1656)
L1-15 (N)	MGAQ-QKYQPLDELDKTLYDQFMLQQG LEGGGGG-Fc (SEQ ID NO: 1657)
L1-2 (N)	MGAQ-LNFTPLDELEQTLYEQWTLQQS LEGGGGG-Fc (SEQ ID NO: 1658)
L1-10 (N)	MGAQ-QKFQPLDELEQTLYEQFMLQQA LEGGGGG-Fc (SEQ ID NO: 1659)
L1-13 (N)	MGAQ-QEYEPLDELDETLYNQWMFHQR LEGGGGG-Fc (SEQ ID NO: 1660)
L1-5 (N)	MGAQ-VKYKPLDELDEILYEQQTFQER LEGGGGG-Fc (SEQ ID NO: 1661)
L1-C2 (N)	MGAQ-TKFQPLDELDQTLYEQWTLQQR LEGGGGG-Fc (SEQ ID NO: 1662)
L1-C3 (N)	MGAQ-TNFQPLDELDQTLYEQWTLQQR LEGGGGG-Fc (SEQ ID NO: 1663)
L1-11 (N)	MGAQ-QNFKPMDELEDTLYKQFLFQHS LEGGGGG-Fc (SEQ ID NO: 1664)
L1-17 (N)	MGAQ-VKYKPLDELDEWLYHQFTLHHQ LEGGGGG-Fc (SEQ ID NO: 1665)
L1-12 (N)	MGAQ-YKFTPLDDLEQTLYEQWTLQHV LEGGGGG-Fc (SEQ ID NO: 1666)
L1-1 (N)	MGAQ-QNYKPLDELDATLYEHFIFHYT LEGGGGG-Fc

	(SEQ ID NO: 1667)
L1-4 (N)	MGAQ-VKFKPLDALEQTLYEHWMFQQA LEGGGGG-Fc (SEQ ID NO: 1668)
L1-20 (N)	MGAQ-EDYMPLDALDAQLYEQFILLHG LEGGGGG-Fc (SEQ ID NO: 1669)
L1-22 (N)	MGAQ-YKFNPMDELEQTLYEEFLFQHA LEGGGGG-Fc (SEQ ID NO: 1670)
L1-14 (N)	MGAQ-SNFMPLDELEQTLYEQFMLQHQ LEGGGGG-Fc (SEQ ID NO: 1671)
L1-16 (N)	MGAQ-QKFQPLDELEETLYKQWTLQQR LEGGGGG-Fc (SEQ ID NO: 1672)
L1-18 (N)	MGAQ-QKFMPLDELDEILYEQFMFQQS LEGGGGG-Fc (SEQ ID NO: 1673)
L1-3 (N)	MGAQ-TKFNPLDELEQTLYEQWTLQHQ LEGGGGG-Fc (SEQ ID NO: 1674)
L1-21 (N)	MGAQ-HTFQPLDELEETLYYQWLYDQL LEGGGGG-Fc (SEQ ID NO: 1675)
L1-C1 (N)	MGAQ-QKFKPLDELEQTLYEQWTLQQR LEGGGGG-Fc (SEQ ID NO: 1676)
L1-19 (N)	MGAQ-QTFQPLDDLEEYLYEQWIRRYH LEGGGGG-Fc (SEQ ID NO: 1677)
L1-9 (N)	MGAQ-SKFKPLDELEQTLYEQWTLQHA LEGGGGG-Fc (SEQ ID NO: 1678)
Con1 Derived Affinity-Matured Pbs	**Peptibody Sequence (Seq Id No:)**
Con1-4 (C)	M-Fc-GGGGGAQ-SGQLRPCEEIFGCGTQNLAL-LE (SEQ ID NO: 1679)
Con1-1 (C)	M-Fc-GGGGGAQ-AGGMRPYDGMLGWPNYDVQA-LE (SEQ ID NO: 1680)
Con1-6 (C)	M-Fc-GGGGGAQ-GQDLRPCEDMFGCGTKDWYG-LE (SEQ ID NO: 1681)
Con1-3 (C)	M-Fc-GGGGGAQ-APGQRPYDGMLGWPTYQRIV-LE (SEQ ID NO: 1682)
Con1-2 (C)	M-Fc-GGGGGAQ-QTWDDPCMHILGPVTWRRCI-LE (SEQ ID NO: 1683)
Con1-5 (C)	M-Fc-GGGGGAQ-FGDKRPLECMFGGPIQLCPR-LE (SEQ ID NO: 1684)
Parent: Con1 (C)	M-Fc-GGGGGAQ-KRPCEEIFGGCTYQ-LE

	(SEQ ID NO: 1685)
12-9 Derived Affinity-Matured Pbs	**Peptibody Sequence (Seq Id No:)**
12-9-3 (C)	M-Fc-GGGGGAQ-LQEWCEGVEDPFTFGCEKQR-LE (SEQ ID NO: 1686)
12-9-7 (C)	M-Fc-GGGGGAQ-MLDYCEGMDDPFTFGCDKQM-LE (SEQ ID NO: 1687)
12-9-6 (C)	M-Fc-GGGGGAQ-HQEYCEGMEDPFTFGCEYQG-LE (SEQ ID NO: 1688)
12-9-C2 (C)	M-Fc-GGGGGAQ-LQDYCEGVEDPFTFGCENQR-LE (SEQ ID NO: 1689)
12-9-5 (C)	M-Fc-GGGGGAQ-LLDYCEGVQDPFTFGCENLD-LE (SEQ ID NO: 1690)
12-9-1 (C)	M-Fc-GGGGGAQ-GFEYCDGMEDPFTFGCDKQT-LE (SEQ ID NO: 1691)
12-9-4 (C)	M-Fc-GGGGGAQ-AQDYCEGMEDPFTFGCEMQK-LE (SEQ ID NO: 1692)
12-9-C1 (C)	M-Fc-GGGGGAQ-LQDYCEGVEDPFTFGCEKQR-LE (SEQ ID NO: 1693)
12-9-2 (C)	M-Fc-GGGGGAQ-KLEYCDGMEDPFTQGCDNQS-LE (SEQ ID NO: 1694)
Parent: 12-9 (C)	M-Fc-GGGGGAQ-FDYCEGVEDPFTFGCDNH-LE (SEQ ID NO: 1695)

[00163] In addition to the TMP compounds set out in Table 6, the invention provides numerous other TMP compounds. In one aspect, TMP compounds comprise the following general structure:

TMP_1-$(L_1)_n$-TMP_2

wherein TMP_1 and TMP_2 are each independently selected from the group of compounds comprising the core structure:

X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10},

wherein,

X_2 is selected from the group consisting of Glu, Asp, Lys, and Val;

X_3 is selected from the group consisting of Gly and Ala;

X_4 is Pro;

X_5 is selected from the group consisting of Thr and Ser;

X_6 is selected from the group consisting of Leu, Ile, Val, Ala, and Phe;

X_7 is selected from the group consisting of Arg and Lys;

X_8 is selected from the group consisting of Gln, Asn, and Glu;

X_9 is selected from the group consisting of Trp, Tyr, and Phe;

X_{10} is selected from the group consisting of Leu, Ile, Val, Ala, Phe, Met, and Lys;

L_1 is a linker as described herein; and

n is 0 or 1;

and physiologically acceptable salts thereof.

[00164] In one embodiment, L_1 comprises $(Gly)_n$, wherein n is 1 through 20, and when n is greater than 1, up to half of the Gly residues may be substituted by another amino acid selected from the remaining 19 natural amino acids or a stereoisomer thereof.

[00165] In addition to the core structure X_2-X_{10} set forth above for TMP_1 and TMP_2, other related structures are also possible wherein one or more of the following is added to the TMP_1 and/or TMP_2 core structure: X_1 is attached to the N-terminus and/or X_{11}, X_{12}, X_{13}, and/or X_{14} are attached to the C-terminus, wherein X_1, X_{12}, X_{13}, and X_{14} are as follows:

X_1 is selected from the group consisting of Ile, Ala, Val, Leu, Ser, and Arg;

X_{11} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Ser, Thr, Lys, His, and Glu;

X_{12} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Gly, Ser, and Gln;

X_{13} is selected from the group consisting of Arg, Lys, Thr, Val, Asn, Gln, and Gly; and

X_{14} is selected from the group consisting of Ala, Ile, Val, Leu, Phe, Thr, Arg, Glu, and Gly.

[00166] TMP compounds of the invention are made up of, i.e., comprising, at least 9 subunits (X_2-X_{10}), wherein X_2-X_{10} comprise the core structure. The X_2-X_{14} subunits are amino acids independently selected from among the 20 naturally-occurring amino acids, however, the invention embraces compounds where X_2-X_{14} are independently selected from the group of atypical, non-naturally occurring amino acids well known in the art. Specific amino acids are identified for each position. For example, X_2 may be Glu, Asp, Lys, or Val.

Both three-letter and single letter abbreviations for amino acids are used herein; in each case, the abbreviations are the standard ones used for the 20 naturally-occurring amino acids or well-known variations thereof. These amino acids may have either L or D stereochemistry (except for Gly, which is neither L nor D), and the TMPs (as well as all other compounds of the invention) may comprise a combination of stereochemistries. The invention also provides reverse TMP molecules (as well as for all other peptides disclosed herein) 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 TMP molecules (as well as for all other molecules of the invention described herein) wherein, like a reverse TMP, the amino terminal to carboxy terminal sequence of amino acids is reversed and residues that are normally "L" enatiomers in TMP are altered to the "D" stereoisomer form.

[00167] Exemplary TMP compounds of the invention therefore include without limitation the following compounds:

IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 993)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)

(SEQ. ID NO: 994)

IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear)

(SEQ. ID NO: 995)

IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 996)

IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 997)

IEGPTLRQWLAARA-GGGK(BrAc)GGGG-IEGPTLRQWLAARA

(SEQ. ID NO: 998)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 999)

IEGPTLRQWLAARA-GGGK(PEG)GGGG-IEGPTLRQWLAARA

(SEQ. ID NO: 1000)

IEGPTLRQWLAARA-GGGC(PEG)GGGG-IEGPTLRQWLAARA

(SEQ. ID NO: 1001)

IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 1002)

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 1003)

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 1004)

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 1005)

Fc-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 1006)

IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA-Fc (SEQ. ID NO: 1007)

Fc-GG-IEGPTLRQWLAARA-GPNG-IEGPTLRQWLAARA (SEQ. ID NO: 1008)

Fc-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 1009)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (cyclic)

(SEQ. ID NO: 1010)

Fc-IEGPTLRQCLAARA-GGGGGGGG-IEGPTLRQCLAARA (linear)

(SEQ. ID NO: 1011)

Fc-IEGPTLRQALAARA-GGGGGGGG-IEGPTLRQALAARA (SEQ. ID NO: 1012)

Fc-IEGPTLRQWLAARA-GGGKGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 1013)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 1014)

Fc-IEGPTLRQWLAARA-GGGNGSGG-IEGPTLRQWLAARA (SEQ. ID NO: 1015)

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA

Fc-IEGPTLRQWLAARA-GGGCGGGG-IEGPTLRQWLAARA (SEQ. ID NO: 1016)

Fc-GGGGG-IEGPTLRQWLAARA-GGGGGGGG-IEGPTLRQWLAARA

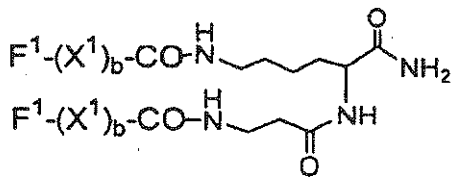
(SEQ. ID NO: 1017)

[00168] **Derivatives**

[00169] The invention also contemplates derivatizing the peptide and/or vehicle portion (as discussed below) of the compounds. Such derivatives may improve the solubility, absorption, biological half life, and the like of the compounds. The moieties may alternatively eliminate or attenuate any undesirable side-effect of the compounds and the like. Exemplary derivatives include compounds in which:

1. The compound or some portion thereof is cyclic. For example, the peptide portion may be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation. For citations to references on preparation of cyclized derivatives, see Table 2.

2. The compound is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion may be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound may also be cross-linked through its C-terminus, as in the molecule shown below.



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.

8. Heterobifunctional polymers are typically used to link proteins. An example is SMCC, or Succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate. The NHS (N-Hyroxylsuccinimide) end reacts with primary amines, which upon conjugation at pH ~ 7 is optimal. Once the complex is formed, reaction of the maleimide portion of SMCC can proceed with another protein/peptide containing a free sulfhydryl group, which occurs at a much faster rate than the formation of the amide in the initial reaction. The result is a link between two proteins, for example, antibody-enzyme conjugates. An application is illustrated by the preparation of crosslinked Fab' fragments to horseradish peroxidase (Ishikwa, et. al., 1983a,b; Yoshitake et al., 1982a,b; Imagawa etal, 1982; Uto et al., 1991). The use of Sulfo SMCC (Sulfosuccinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate) allows for water solubility so that an organic solubilization step is not needed, allowing for greater flexibility and less disruption of activity in reacting with proteins.

[00170] Lysinyl residues and amino terminal residues may be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate.

[00171] Arginyl residues may be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

[00172] Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole

and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively.

[00173] 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-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues may be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

[00174] Glutaminyl and asparaginyl residues may be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

[00175] Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9.

[00176] Derivatization with bifunctional agents is useful for cross-linking the peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

[00177] Carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins. Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by

virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

[00178] 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).

[00179] 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.

[00180] 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).

[00181] 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.

[00182] Useful conjugation partners include:

- 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);

- biotin, streptavidin (useful as either partner molecules in capture systems or as tracers, especially for diagnostic use); and
- cytotoxic agents (e.g., doxorubicin).

[00183] 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.

[00184] 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.

[00185] **Vehicles**

[00186] The invention requires the presence of at least one vehicle attached to a peptide through the N-terminus, C-terminus or a sidechain of one of the amino acid residues. Multiple vehicles may also be used. In one aspect, an Fc domain is the vehicle. The Fc domain may be fused to the N or C termini of the peptides or at both the N and C termini.

[00187] In various embodiments of the invention, the Fc component is either a native Fc or an Fc variant. The immunoglobulin source of the native Fc is, in one aspect, of human origin and may, in alternative embodiments, be of any class of immunoglobulin. Native Fc domains are made up of monomeric polypeptides that may be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and/or non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc

molecules ranges from one to four 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).

[00188] It should be noted that Fc monomers will spontaneously dimerize when the appropriate cysteine residues are present, unless particular conditions are present that prevent dimerization through disulfide bond formation. Even if the cysteine residues that normally form disulfide bonds in the Fc dimer are removed or replaced by other residues, the monomeric chains will generally form a dimer through non-covalent interactions. The term "Fc" herein is used to mean any of these forms: the native monomer, the native dimer (disulfide bond linked), modified dimers (disulfide and/or non-covalently linked), and modified monomers (i.e., derivatives).

[00189] As noted, Fc variants are suitable vehicles within the scope of this invention. A native Fc may be extensively modified to form an Fc variant, provided binding to the salvage receptor is maintained; see, for example WO 97/34631 and WO 96/32478. In such Fc variants, one may 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 acids, such as peptidomimetics or D-amino acids. Fc variants may be desirable for a number of reasons, several of which are described herein. 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). 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.

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.

7. The ADCC site is removed. ADCC sites are known in the art; see, for example, Molec. Immunol. 29 (5): 633-9 (1992) with regard to ADCC sites in IgG1. These sites, as well, are not required for the fusion molecules of the present invention and so may be removed.

8. When the native Fc is derived from a non-human antibody, the native Fc may be humanized. Typically, to humanize a native Fc, one will substitute selected residues in the non-human native Fc with residues that are normally found in human native Fc. Techniques for antibody humanization are well known in the art.

[00190] An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic 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 "vehicle" and are within the scope of 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).

[00191] Variants, analogs or derivatives of the Fc portion may be constructed by, for example, making various substitutions of residues or sequences.

[00192] Variant (or analog) polypeptides include insertion variants, wherein one or more amino acid residues supplement an Fc amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the Fc amino acid sequence. Insertion variants, with additional residues at either or both termini, can include for example, fusion proteins and proteins including amino acid tags or labels. For example, the Fc molecule may optionally contain an N-terminal Met, especially when the molecule is expressed recombinantly in a bacterial cell such as E. coli.

[00193] In Fc deletion variants, one or more amino acid residues in an Fc polypeptide are removed. Deletions can be effected at one or both termini of the Fc polypeptide, or with removal of one or more residues within the Fc amino acid sequence. Deletion variants, therefore, include all fragments of an Fc polypeptide sequence.

[00194] In Fc substitution variants, one or more amino acid residues of an Fc polypeptide are removed and replaced with alternative residues. In one aspect, the substitutions are conservative in nature and conservative substitutions of this type are well known in the art. Alternatively, the invention embraces substitutions that are also non-conservative. Exemplary conservative substitutions are described in Lehninger, [*Biochemistry*, 2nd Edition; Worth Publishers, Inc.New York (1975), pp.71-77] and set out immediately below.

CONSERVATIVE SUBSTITUTIONS I

SIDE CHAIN CHARACTERISTIC	AMINO ACID
Non-polar (hydrophobic):	
A. Aliphatic	A L I V P
B. Aromatic	F W
C. Sulfur-containing	M
D. Borderline	G
Uncharged-polar:	
A. Hydroxyl	S T Y
B. Amides	N Q
C. Sulfhydryl	C
D. Borderline	G
Positively charged (basic)	K R H
Negatively charged (acidic)	D E

[00195] Alternative, exemplary conservative substitutions are set out immediately below.

CONSERVATIVE SUBSTITUTIONS II

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

[00196] For example, cysteine residues can be deleted or replaced with other amino acids to prevent formation of some or all disulfide crosslinks of the Fc sequences. Each cysteine residue can be removed and/or substituted with other amino acids, such as Ala or Ser. As another example, modifications may also be made to introduce amino acid substitutions to (1) ablate the Fc receptor binding site; (2) ablate the complement (C1q) binding site; and/or to (3) ablate the antibody dependent cell-mediated cytotoxicity (ADCC) site. Such sites are known in the art, and any known substitutions are within the scope of Fc as used herein. For example, see Molecular Immunology, Vol. 29, No. 5, 633-639 (1992) with regard to ADCC sites in IgG1.

[00197] Likewise, one or more tyrosine residues can be replaced by phenylalanine residues. In addition, other variant amino acid insertions, deletions and/or substitutions are also contemplated and are within the scope of the present invention. Conservative amino acid substitutions will generally be preferred. Furthermore, alterations may be in the form of altered amino acids, such as peptidomimetics or D-amino acids.

[00198] Fc sequences of the compound may also be derivatized as described herein for peptides, i.e., bearing modifications other than insertion, deletion, or substitution of amino acid residues. Preferably, the modifications are covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Derivatives of the invention may be prepared to increase circulating half-life, or may be designed to improve targeting capacity for the polypeptide to desired cells, tissues, or organs.

[00199] It is also possible to use the salvage receptor binding domain of the intact Fc molecule as the Fc part of a compound of the invention, such as described in WO 96/32478, entitled "Altered Polypeptides with Increased Half-Life." Additional members of the class of molecules designated as Fc herein are those that are described in WO 97/34631, entitled "Immunoglobulin-Like Domains with Increased Half-Lives." Both of the published PCT applications cited in this paragraph are hereby incorporated by reference.

[00200] **WSP components**

[00201] Compounds of the invention may further include at least one WSP. The WPS moiety of the molecule may be branched or unbranched. For therapeutic use of the end-product preparation, the polymer is pharmaceutically acceptable. In general, a desired polymer is selected based on such considerations as whether the polymer conjugate will be used therapeutically, and if so, the desired dosage, circulation time, resistance to proteolysis, and other considerations. In various aspects, the average molecular weight of each water soluble polymer is between about 2 kDa and about 100 kDa, between about 5 kDa and about 50 kDa, between about 12 kDa and about 40 kDa and between about 20 kDa and about 35 kDa. In yet another aspect the molecular weight of each polymer is between about 6 kDa and about 25 kDa. The term "about" as used herein and throughout, indicates that in preparations of a water soluble polymer, some molecules will weigh more, some less, than the stated molecular weight. Generally, the higher the molecular weight or the more branches, the higher the polymer/protein ratio. Other sizes may be used, depending on the desired therapeutic profile including for example, the duration of sustained release; the effects, if any, on biological activity; the ease in handling; the degree or lack of antigenicity and other known effects of a water soluble polymer on a therapeutic protein.

[00202] The WSP should be attached to a polypeptide or peptide with consideration given to effects on functional or antigenic domains of the polypeptide or peptide. In general, chemical derivatization may be performed under any suitable condition used to react a protein with an activated polymer molecule. Activating groups which can be used to link the water soluble polymer to one or more proteins include without limitation sulfone, maleimide,

sulfhydryl, thiol, triflate, tresylate, azidirine, oxirane and 5-pyridyl. If attached to the peptide by reductive alkylation, the polymer selected should have a single reactive aldehyde so that the degree of polymerization is controlled.

[00203] Suitable, clinically acceptable, water soluble polymers include without limitation, PEG, polyethylene glycol propionaldehyde, copolymers of ethylene glycol/propylene glycol, monomethoxy-polyethylene glycol, carboxymethylcellulose, polyacetals, polyvinyl alcohol (PVA), polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, poly (.beta.-amino acids) (either homopolymers or random copolymers), poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers (PPG) and other polyakylene oxides, polypropylene oxide/ethylene oxide copolymers, polyoxyethylated polyols (POG) (e.g., glycerol) and other polyoxyethylated polyols, polyoxyethylated sorbitol, or polyoxyethylated glucose, colonic acids or other carbohydrate polymers, Ficoll or dextran and mixtures thereof.

[00204] Water Soluble Polymers can also be made to be thermally sensitive, as in the formation of reverse thermal gels. Examples include Tetronics, with tetra armed backbones, and PEG-PLGA copolymers. The hydrophilicity of polymers can be varied by substituting hydrophobic portions into the polymer chain. An example of this is in the manufacture of PLGA, in which the ratio of lactic acid to glycolic acid can be increased to allow for lower water solubility. Lower water soluble polymers may be desired in certain applications, for example in increasing the potential to interact with cell membranes. Upon reconstitution, an appropriate ratio of phospholipids may be used to induce the formation of micelles or liposomes in solution. The advantage of such a system may be in the ability to incorporate some of the protein within the micelle, with the potential benefit of prolonging delivery. Phospholipids capable of forming liposomes or micelles include DMPG, DMPC, DOPC, DOPG and apprpopriate secondary liposome strengthening components such as cholesterol. Certain excipients, such as DEA oleth-10 phosphate and oleth 10-phosphate, are capable of forming micelles in solution.

[00205] Polysaccharide polymers are another type of water soluble polymer which may be used for protein or peptide modification. Modifying proteins or peptides by adding polysaccharide(s) , e.g., glycosylation, may increase half-life, decrease antigenicity, increase stability and decrease proteolysis. Dextrans are polysaccharide polymers comprised of individual subunits of glucose predominantly linked by α1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights

from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use in the present invention 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. 0 315 456, 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.

[00206] In one embodiment, the WSP is PEG and the invention contemplates preparations wherein a compound is modified to include any of the forms of PEG that have been used to derivatize other proteins, such as and without limitation mono-(C1-C10) alkoxy- or aryloxy-polyethylene glycol. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The PEG group may be of any convenient molecular weight and may be linear or branched. The average molecular weight of PEG contemplated for use in the invention ranges from about 2 kDa to about 100 kDa, from about 5 kDa to about 50 kDa, from about 5 kDa to about 10 kDa. In another aspect, the PEG moiety has a molecular weight from about 6 kDa to about 25 kDa. PEG groups generally are attached to peptides or proteins via acylation or reductive alkylation through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the target peptide or protein (e.g., an aldehyde, amino, or ester group). Using methods described herein, a mixture of polymer/peptide conjugate molecules can be prepared, and the advantage provided herein is the ability to select the proportion of polymer/peptide conjugate to include in the mixture. Thus, if desired, a mixture of peptides with various numbers of polymer moieties attached (i.e., zero, one or two) can be prepared with a predetermined proportion of polymer/protein conjugate.

[00207] A useful strategy for the PEGylation (other methods are discussed in more detail herein) 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. 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.

[00208] Linkers

[00209] Any "linker" group is optional, whether positioned between peptides, peptide and vehicle or vehicle and WSP. 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, (Gly)8, poly(Gly-Ala), and polyalanines. Other specific examples of linkers are:

(Gly)3Lys(Gly)4 (SEQ ID NO: 1018);

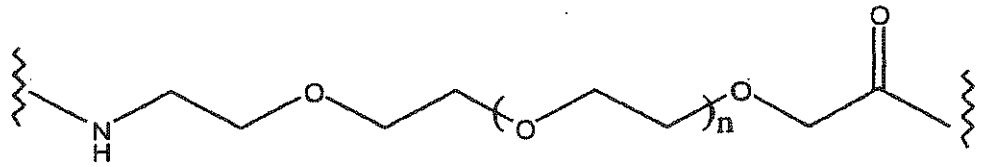
(Gly)3AsnGlySer(Gly)2 (SEQ ID NO: 1019);

(Gly)3Cys(Gly)4 (SEQ ID NO: 1020); and

GlyProAsnGlyGly (SEQ ID NO: 1021).

[00210] 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.

[00211] Non-peptide linkers are also possible. For example, alkyl linkers such as -NH-(CH2)s-C(O)-, wherein s = 2-20 could be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C1-C6) lower acyl, halogen (e.g., Cl, Br), CN, NH2, phenyl, etc. An exemplary non-peptide linker is a PEG linker,



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.

[00212] Polypeptide and Peptide production

[00213] A peptide having been identified may be made in transformed host cells using recombinant DNA techniques. If the vehicle component is a polypeptide, the polypeptide- or peptide-vehicle fusion product may be expressed as one. To do so, a recombinant DNA molecule encoding the peptide is first prepared using methods 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 therefore provides polynucleotides encoding a compound of the invention.

[00214] The invention also provides vectors encoding compounds of the invention in an appropriate host. The vector comprises the polynucleotide that encodes the compound operatively linked to appropriate expression control sequences. Methods of effecting this operative linking, either before or after the polynucleotide 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.

[00215] The resulting vector having the polynucleotide therein is used to transform an appropriate host. This transformation may be performed using methods well known in the art.

[00216] 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), yeast (such as Saccharomyces) and other fungi, insects, plants, mammalian (including human) cells in culture, or other hosts known in the art.

[00217] Next, the transformed host is cultured and purified. Host cells may 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.

[00218] Depending on the host cell utilized to express a compound of the invention, carbohydrate (oligosaccharide) groups may conveniently be attached to sites that are known to be glycosylation sites in proteins. Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids not counting proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, may confer acidic properties to the glycosylated compound. Such site(s) may be incorporated in the linker of the compounds of this invention and are preferably glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites may further be glycosylated by synthetic or semi-synthetic procedures known in the art.

[00219] Alternatively, the compounds may be made by synthetic methods. For 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 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.

[00220] Compounds that contain derivatized peptides or which contain non-peptide groups are particularly amendable to synthesis by well-known organic chemistry techniques.

[00221] **WSP modification**

[00222] For obtaining a compound covalently attached to a WSP, any method described herein or otherwise known in the art is employed. Methods for preparing chemical derivatives of polypeptides or peptides will generally comprise the steps of (a) reacting the peptide with the activated polymer molecule (such as a reactive ester or aldehyde derivative of the polymer molecule) under conditions whereby the polypeptide becomes attached to one or more polymer molecules, and (b) obtaining the reaction product(s). The optimal reaction conditions will be determined based on known parameters and the desired result. For

example, the larger the ratio of polymer molecules:protein, the greater the percentage of attached polymer molecule.

[00223] A biologically active molecule can be linked to a polymer through any available functional group using standard methods well known in the art. Examples of functional groups on either the polymer or biologically active molecule which can be used to form such linkages include amine and carboxy groups, thiol groups such as in cysteine resides, aldehydes and ketones, and hydroxy groups as can be found in serine, threonine, tyrosine, hydroxyproline and hydroxylysine residues.

[00224] The polymer can be activated by coupling a reactive group such as trichloro-s-triazine [Abuchowski, et al., (1977), J. Biol. Chem. 252:3582-3586, incorporated herein by reference in its entirety], carbonylimidazole [Beauchamp, et al., (1983), Anal. Biochem. 131:25-33, incorporated herein by reference in its entirety], or succinimidyl succinate [Abuchowski, et al., (1984), Cancer Biochem. Biophys. 7:175-186, incorporated herein by reference in its entirety] in order to react with an amine functionality on the biologically active molecule. Another coupling method involves formation of a glyoxylyl group on one molecule and an aminooxy, hydrazide or semicarbazide group on the other molecule to be conjugated [Fields and Dixon, (1968), Biochem. J. 108:883-887; Gaertner, et al., (1992), Bioconjugate Chem. 3:262-268; Geoghegan and Stroh, (1992), Bioconjugate Chem. 3:138-146; Gaertner, et al., (1994), J. Biol. Chem. 269:7224-7230, each of which is incorporated herein by reference in its entirety]. Other methods involve formation of an active ester at a free alcohol group of the first molecule to be conjugated using chloroformate or disuccinimidylcarbonate, which can then be conjugated to an amine group on the other molecule to be coupled [Veronese, et al., (1985), Biochem. and Biotech. 11:141-152; Nitecki, et al., U.S. Patent No. 5,089,261; Nitecki, U.S. Patent No. 5,281,698, each of which is incorporated herein by reference in its entirety]. Other reactive groups which may be attached via free alcohol groups are set forth in Wright, EP 0539167A2 (incorporated herein by reference in its entirety), which also describes the use of imidates for coupling via free amine groups.

[00225] Another chemistry involves acylation of the primary amines of a target using the NHS-ester of methoxy-PEG (O-[(N-succinimidyloxycarbonyl)-methyl]-O'-methylpolyethylene glycol). Acylation with methoxy-PEG-NHS results in an amide linkage which will eliminate the charge from the original primary amine. Other methods utilize mild oxidation of a target under conditions selected to target the pendant diol of the penultimate glycosyl unit sialic acid for oxidation to an aldehyde. The resultant glycoaldehyde was then

reacted with a methoxy-PEG-hydrazide (O-(Hydrazinocarbonylmethyl)-O'-methylpolyethylene glycol) to form a semi-stable hydrazone between PEG and target. The hydrazone is subsequently reduced by sodium cyanoborohydride to produce a stable PEG conjugate. See for example, U.S. Patent No. 6,586,398 (Kinstler, et al., July 1, 2003), incorporated herein by reference in its entirety.

[00226] In specific applications of techniques for chemical modification, for example, U.S. Patent No. 4,002,531 (incorporated herein by reference in its entirety) states that reductive alkylation was used for attachment of polyethylene glycol molecules to an enzyme. U.S. Patent No. 4,179,337 (incorporated herein by reference in its entirety) discloses PEG:protein conjugates involving, for example, enzymes and insulin. U.S. Patent No. 4,904,584 (incorporated herein by reference in its entirety) discloses the modification of the number of lysine residues in proteins for the attachment of polyethylene glycol molecules via reactive amine groups. U.S. Patent No. 5,834,594 (incorporated herein by reference in its entirety) discloses substantially non-immunogenic water soluble PEG:protein conjugates, involving for example, the proteins IL-2, interferon alpha, and IL-1ra. The methods of Hakimi et al. involve the utilization of unique linkers to connect the various free amino groups in the protein to PEG. U.S. Patent Nos. 5,824,784 and 5,985,265 (each of which is incorporated herein by reference in its entirety) teach methods allowing for selectively N-terminally chemically modified proteins and analogs thereof, including G-CSF and consensus interferon. Importantly, these modified proteins have advantages as relates to protein stability, as well as providing for processing advantages.

[00227] WSP modification is also described in Francis et al., In: Stability of protein pharmaceuticals: *in vivo* pathways of degradation and strategies for protein stabilization (Eds. Ahern., T. and Manning, M. C.) Plenum, N. Y., 1991 (incorporated herein by reference in its entirety), is used. In still another aspect, the method described in Delgado et al., "Coupling of PEG to Protein By Activation With Tresyl Chloride, Applications In Immunoaffinity Cell Preparation", In: Fisher et al., eds., Separations Using Aqueous Phase Systems, Applications In Cell Biology and Biotechnology, Plenum Press, N.Y., N.Y., 1989 pp. 211-213 (incorporated herein by reference in its entirety), which involves the use of tresyl chloride, which results in no linkage group between the WSP moiety and the polypeptide moiety. In other aspects, attachment of a WSP is effected through use of N-hydroxy succinimidyl esters of carboxymethyl methoxy polyethylene glycol, as well known in the art.

[00228] For other descriptions of modification of a target with a WSP, see, for example, U.S patent application No. 20030096400; EP 0 442724A2; EP 0154316; EP

0401384; WO 94/13322; U.S. Patent Nos. 5,362,852; 5,089,261; 5,281,698; 6,423,685; 6,635,646; 6,433,135; International application WO 90/07938; Gaertner and Offord, (1996), Bioconjugate Chem. 7:38-44; Greenwald et al., Crit Rev Therap Drug Carrier Syst. 2000;17:101-161; Kopecek et al., J Controlled Release., 74:147-158, 2001; Harris et al., Clin Pharmacokinet. 2001;40(7):539-51; Zalipsky et al., Bioconjug Chem. 1997;8:111-118; Nathan et al., Macromolecules. 1992;25:4476-4484; Nathan et al., Bioconj Chem. 1993;4:54-62; and Francis *et al.*, *Focus on Growth Factors*, 3:4-10 (1992), the disclosures of which are incorporated herein by reference in their entirety.

[00229] **Reductive alkylation**

[00230] In one aspect, covalent attachment of a WSP is carried out by reductive alkylation chemical modification procedures as provided herein to selectively modify the N-terminal α-amino group, and testing the resultant product for the desired biological characteristic, such as the biological activity assays provided herein.

[00231] Reductive alkylation for attachment of a WSP to a protein or peptide exploits differential reactivity of different types of primary amino groups (e.g., lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[00232] For reductive alkylation, the polymer(s) selected could have a single reactive aldehyde group. A reactive aldehyde is, for example, polyethylene glycol propionaldehyde, which is water stable, or mono C_1-C_{10} alkoxy or aryloxy derivatives thereof (see U.S. Patent No. 5,252,714, incorporated herein by reference in its entirety). In one approach, reductive alkylation is employed to conjugate a PEG-aldehyde (O-(3-Oxopropyl)-O'-methylpolyethylene glycol) to a primary amine. Under appropriate conditions, this approach has been demonstrated to yield PEG conjugates predominately modified through the α-amine at the protein N-terminus.

[00233] An aldehyde functionality useful for conjugating the biologically active molecule can be generated from a functionality having adjacent amino and alcohol groups. In a polypeptide, for example, an N-terminal serine, threonine or hydroxylysine can be used to generate an aldehyde functionality via oxidative cleavage under mild conditions using periodate. These residues, or their equivalents, can be normally present, for example at the N-terminus of a polypeptide, may be exposed via chemical or enzymatic digestion, or may be introduced via recombinant or chemical methods. The reaction conditions for generating the aldehyde typically involve addition of a molar excess of sodium meta periodate and under

mild conditions to avoid oxidation at other positions in the protein. The pH is preferably about 7.0. A typical reaction involves the addition of a 1.5 fold molar excess of sodium meta periodate, followed by incubation for 10 minutes at room temperature in the dark.

[00234] The aldehyde functional group can be coupled to an activated polymer containing a hydrazide or semicarbazide functionality to form a hydrazone or semicarbazone linkage. Hydrazide-containing polymers are commercially available, and can be synthesized, if necessary, using standard techniques. PEG hydrazides for use in the invention can be obtained from Shearwater Polymers, Inc., 2307 Spring Branch Road, Huntsville, Ala. 35801 (now part of Nektar Therapeutics, 150 Industrial Road, San Carlos, CA 94070-6256). The aldehyde is coupled to the polymer by mixing the solution of the two components together and heating to about 37°C until the reaction is substantially complete. An excess of the polymer hydrazide is typically used to increase the amount of conjugate obtained. A typical reaction time is 26 hours. Depending on the thermal stability of the reactants, the reaction temperature and time can be altered to provide suitable results. Detailed determination of reaction conditions for both oxidation and coupling is set forth in Geoghegan and Stroh, (1992), Bioconjugate Chem. 3:138-146, and in Geoghegan, U.S. Patent No. 5,362,852, each of which is incorporated herein by reference in its entirety.

[00235] Using reductive alkylation, the reducing agent should be stable in aqueous solution and preferably be able to reduce only the Schiff base formed in the initial process of reductive alkylation. Reducing agents are selected from, and without limitation, sodium borohydride, sodium cyanoborohydride, dimethylamine borate, trimethylamine borate and pyridine borate.

[00236] The reaction pH affects the ratio of polymer to protein to be used. In general, if the reaction pH is lower than the pK_a of a target reactive group, a larger excess of polymer to protein will be desired. If the pH is higher than the target pK_a, the polymer:protein ratio need not be as large (i.e., more reactive groups are available, so fewer polymer molecules are needed).

[00237] Accordingly, the reaction is performed in one aspect at a pH which allows one to take advantage of the pK_a differences between the ε-amino groups of the lysine residues and that of the α-amino group of the N-terminal residue of the protein. By such selective derivatization, attachment of a water soluble polymer to a protein is controlled; the conjugation with the polymer takes place predominantly at the N-terminus of the protein and no significant modification of other reactive groups, such as the lysine side chain amino groups, occurs.

[00238] In one aspect, therefore, methods are provided for covalent attachment of a WSP to a target compound and which provide a substantially homogenous preparation of WSP/protein conjugate molecules, in the absence of further extensive purification as is required using other chemical modification chemistries. More specifically, if polyethylene glycol is used, methods described allow for production of an N-terminally PEGylated protein lacking possibly antigenic linkage groups, i.e., the polyethylene glycol moiety is directly coupled to the protein moiety without potentially toxic by-products.

[00239] Depending on the method of WSP attachment chosen, the proportion of WSP molecules attached to the target peptide or protein molecule will vary, as will their concentrations in the reaction mixture. In general, the optimum ratio (in terms of efficiency of reaction in that there is no excess unreacted protein or polymer) is determined by the molecular weight of the WSP selected. In addition, when using methods that involve non-specific attachment and later purification of a desired species, the ratio may depend on the number of reactive groups (typically amino groups) available.

[00240] **Purification**

[00241] The method of obtaining a substantially homogeneous WSP-modified preparation is, in one aspect, by purification of a predominantly single species of modified compound from a mixture of species. By way of example, a substantially homogeneous species is first separated by ion exchange chromatography to obtain material having a charge characteristic of a single species (even though other species having the same apparent charge may be present), and then the desired species is separated using size exclusion chromatography. Other methods are reported and contemplated by the invention, includes for example, PCT WO 90/04606, published May 3, 1990, which describes a process for fractionating a mixture of PEG-protein adducts comprising partitioning the PEG/protein adducts in a PEG-containing aqueous biphasic system.

[00242] Thus, one aspect of the present invention is a method for preparing a WSP-modified compound conjugate comprised of (a) reacting a compound having more than one amino group with a water soluble polymer moiety under reducing alkylation conditions, at a pH suitable to selectively activate the α-amino group at the amino terminus of the protein moiety so that said water soluble polymer selectively attaches to said α-amino group; and (b) obtaining the reaction product. Optionally, and particularly for a therapeutic product, the reaction products are separated from unreacted moieties.

[00243] As ascertained by peptide mapping and N-terminal sequencing, a preparation is provided which comprises at least 50% PEGylated peptide in a mixture of PEGylated

peptide and unreacted peptide. In other embodiments, preparations are provided which comprises at least 75% PEGylated peptide in a mixture of PEGylated peptide and unreacted peptide; at least 85% PEGylated peptide in a mixture of PEGylated peptide and unreacted peptide; at least 90% PEGylated peptide in a mixture of PEGylated peptide and unreacted peptide; at least 95% PEGylated peptide in a mixture of PEGylated peptide and unreacted peptide; and at least 99% PEGylated peptide in a mixture of PEGylated peptide and unreacted peptide.

[00244] The following examples are not intended to be limiting but only exemplary of specific embodiments of the invention.

Example 1

mFc-TMP Expression Construct Assembly

[00245] A polynucleotide encoding a TMP fusion protein comprising a murine Fc region (mFc-TMP) was constructed by combining nucleotide sequences individually encoding murine Fc and a TMP (described in EP01124961A2). In the first round of PCR, the murine Fc-encoding component was amplified with PCR primers 3155-58 (SEQ ID NO: 1022) and 1388-00 (SEQ ID NO: 1023).

3155-58: CCGGGTAAAGGTGGAGGTGGTGGTATCGA (SEQ ID NO: 1024)

3155-59: CCACCTCCACCTTTACCCGGAGAGTGGGAG (SEQ ID NO: 1025)

[00246] In a separate reaction, a TMP-encoding polynucleotide was amplified with primers 1209-85 (SEQ ID NO: 1026) and 3155-59 (SEQ ID NO: 1027).

1209-85: CGTACAGGTTTACGCAAGAAAATGG (SEQ ID NO: 1028)

1388-00: CTAGTTATTGCTCAGCGG (SEQ ID NO: 1029)

[00247] The resulting PCR fragments were gel purified and combined in a single tube for a second round of PCR with primers 1209-85 (SEQ ID NO: 1030) and 1388-00 (SEQ ID NO: 1031). The PCR product from this second round of amplification was gel purified and digested with restriction enzymes *Nde*I and *Xho*I. The digestion fragment was purified and ligated into the vector pAMG21, previously digested with the same enzymes. This ligation mix was transformed via electroporation into *E. coli* and plated onto LB + Kanamycin media. Colonies were screened via PCR and DNA sequencing. A positive clone with a

nucleotide sequence (SEQ ID NO: 1032) encoding the mFc-TMP fusion protein (SEQ ID NO: 1033) was identified and designated 6397.

[00248] Murine Fc-TMP fusion protein-encoding polynucleotide (SEQ ID NO: 1034)

```
       1  GATTTGATTC TAGATTTGTT TTAACTAATT AAAGGAGGAA TAACAT

Open RF:
      ATGGTCGACGGTTG TAAGCCATGC ATTTGTACAG TCCCAGAAGT ATCATCTGTC

     101  TTCATCTTCC CCCCAAAGCC CAAGGATGTG CTCACCATTA CTCTGACTCC

     151  TAAGGTCACG TGTGTTGTGG TAGACATCAG CAAGGATGAT CCCGAGGTCC

     201  AGTTCAGCTG GTTTGTAGAT GATGTGGAGG TGCACACAGC TCAGACGCAA

     251  CCCCGGGAGG AGCAGTTCAA CAGCACTTTC CGCTCAGTCA GTGAACTTCC

     301  CATCATGCAC CAGGACTGGC TCAATGGCAA GGAGTTCAAA TGCAGGGTCA

     351  ACAGTGCAGC TTTCCCTGCC CCCATCGAGA AAACCATCTC CAAAACCAAA

     401  GGCAGACCGA AGGCTCCACA GGTGTACACC ATTCCACCTC CCAAGGAGCA

     451  GATGGCCAAG GATAAAGTCA GTCTGACCTG CATGATAACA GACTTCTTCC

     501  CTGAAGACAT TACTGTGGAG TGGCAGTGGA ATGGGCAGCC AGCGGAGAAC

     551  TACAAGAACA CTCAGCCCAT CATGGACACA GATGGCTCTT ACTTCGTCTA

     601  CAGCAAGCTC AATGTGCAGA AGAGCAACTG GGAGGCAGGA AATACTTTCA

     651  CCTGCTCTGT GTTACATGAG GGCCTGCACA ACCACCATAC TGAGAAGAGC

     701  CTCTCCCACT CTCCGGGTAA AGGTGGAGGT GGTGGTATCG AAGGTCCGAC

     751  TCTGCGTCAG TGGCTGGCTG CTCGTGCTGG TGGTGGAGGT GGCGGCGGAG

     801  GTATTGAGGG CCCAACCCTT CGCCAATGGC TTGCAGCACG CGCATAA
```

3' Sequence:

TCTCGAGGATCCG CGGAAAGAAG AAGAAGAAGA AGAAAGCCCG AAAGG

[00249] Murine Fc-TMP protein sequence (SEQ ID NO: 1035)

```
  1  MVDGCKPCIC TVPEVSSVFI FPPKPKDVLT ITLTPKVTCV VVDISKDDPE

 51  VQFSWFVDDV EVHTAQTQPR EEQFNSTFRS VSELPIMHQD WLNGKEFKCR

101  VNSAAFPAPI EKTISKTKGR PKAPQVYTIP PPKEQMAKDK VSLTCMITDF

151  FPEDITVEWQ WNGQPAENYK NTQPIMDTDG SYFVYSKLNV QKSNWEAGNT

201  FTCSVLHEGL HNHHTEKSLS HSPGKGGGGG IEGPTLRQWL AARAGGGGGG

251  GGIEGPTLRQ WLAARA*
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Example 2

Fermentation of Strain 6397

[00250] Fermentation of strain 6397 was initiated by inoculation of 500 mL of sterilized Luria broth with a seed culture of the strain in a shake flask. When cell density reached 0.9 at 600 nm, the contents were used to inoculate a 15 L fermentor containing 10 L of complex based growth medium (800 g glycerol, 500 g trypticase, 3 g sodium citrate, 40 g KH_2PO_4, 20 g $(NH_4)_2SO_4$, 5 ml Fluka P-2000 antifoam, 10 ml trace metals (ferric chloride 27.0 g/L, zinc chloride 2.00 g/L, cobalt chloride 2.00 g/L, sodium molybdate 2.00 g/L, calcium chloride 1.00 g/L, cupric sulfate 1.90 g/L, boric acid 0.50 g/L, manganese chloride 1.60 g/L, sodium citrate dihydrate 73.5 g/L), 10 ml vitamins (biotin 0.060 g/L, folic acid 0.040 g/L, riboflavin 0.42 g/L, pyridoxine HCl 1.40 g/L, niacin 6.10 g/L, pantothenic acid 5.40 g/L, sodium hydroxide 5.30 ml/L), add water to bring to 10 L). The fermenter was maintained at 37°C and pH 7 with dissolved oxygen levels kept at a minimum of 30% saturation. When the cell density reached 13.1 OD units at 600 nm, the culture was induced by the addition 10 ml of 0.5 mg/ml N-(3-oxo-hexanoyl) homoserine lactone. At 6 hours post induction, the broth was chilled to 10°C, and the cells were harvested by centrifugation at 4550g for 60 min at 5°C. The cell paste was then stored at –80°C.

Example 3

Protein Refolding

[00251] *E. coli* paste (300 g) from strain 6397 expressing mFc-TMP was dissolved in 2250 ml lysis buffer (50 mM Tris HCl, 5 mM EDTA, pH 8.0) and passed through a chilled microfluidizer two times at 13,000 PSI. The homogenate was then centrifuged at 11,300g for 60 minutes at 4°C. The supernatant was discarded, and the pellet was resuspended in 2400 ml of water using a tissue grinder. The homogenate was then centrifuged at 11,300g for 60 minutes at 4°C. The supernatant was discarded, and the pellet was resuspended in 200 ml volumes of water using a tissue grinder. The homogenate was centrifuged at 27,200g for 30 minutes at 4 °C, and the supernatant was discarded. About 12.5% of the pellet was resuspended in 28 ml 20 mM Tris HCl, pH 8.0, with 35 mg hen egg white lysozyme (Sigma, St Louis, MO) using a tissue grinder and incubated at 37°C for 20 min. Following incubation, the suspension was centrifuged at 27,200g for 30 minutes at 22°C, and the supernatant was discarded. The pellet was resuspended in 35 ml 8 M guanidine HCl, 50 mM Tris HCl, pH 8.0, after which 350 µl 1 M DTT (Sigma, St Louis, MO) was added and material was incubated at 37 °C for 30 minutes. The solution was then centrifuged at 27,200g for 30 minutes at 22°C. The supernatant was then transferred to 3.5 L of refolding buffer (50 mM Tris base, 160 mM arginine HCl, 3 M urea, 20% glycerol, pH 9.5, 1 mM cysteine, 1 mM cystamine HCl) at 1 ml/min with gentle stirring at 4°C.

Example 4

Construct Purification

[00252] After about 40 hours incubation at 4°C with gentle agitation, the refold solution described in Example 3 was concentrated to 500 µl using a tangential flow ultrafiltration apparatus with a 30 kDa cartridge (Satorius,Goettingen, Germany) followed by diafiltration against 3 L of Q-Buffer A (20 mM Tris HCl, pH 8.0). The concentrated material was filtered through a Whatman GF/A filter and loaded on to an 86 ml Q-Sepharose fast flow column (2.6 cm ID) (Amersham Biosciences, Piscataway, NJ) at 15 ml/min. After washing the resin with several column volumes of Q-Buffer A, the protein was eluted using a 20 column volume linear gradient to 60% Q-Buffer B (20 mM Tris HCl, 1 M NaCl, pH 8.0) at 10 ml/min. The peak fractions were pooled, and the pool was passed through a Mustang E syringe filter (Pall Corporation, East Hills, NY) at 1 ml/min. The filtered material was

filtered a second time through a 0.22 μm cellulose acetate filter and stored at –80°C.

Example 5

Protein PEGylation

[00253] To a cooled (4°C), stirred solution of mFc-TMP (3.5 ml, 0.8 mg/ml) in a 100 mM sodium acetate buffer, pH 5, containing 20 mM $NaCNBH_3$, was added a 3.8-fold molar excess of methoxypolyethylene glycol aldehyde (MPEG) (average molecular weight, 20 kDa) (Nektar). The stirring of the reaction mixture was continued at the same temperature. The extent of the protein modification during the course of the reaction was monitored by SEC HPLC using a Superose 6 HR 10/30 column (Amersham Biosciences) eluted with a 0.05 M phosphate buffer with 0.15 M NaCl, pH 7.0 at 0.4 ml/min. After 16 hours the SEC HPLC analysis indicated that the majority of the protein has been conjugated to MPEG. At this time the reaction mixture was buffer-exchanged into a 20 mM Tris/HCl buffer, pH 8.12. The MPEG-mFc-AMP2 conjugates were isolated by ion exchange chromatography using a 1 ml Hi Trap HP Q column (Amersham Biosciences) equilibrated with a 20 mM Tris/HCl buffer, pH 8.12. The reaction mixture was loaded on the column at a flow rate of 0.5 ml/min and the unreacted MPEG aldehyde was eluted with three column volumes of the starting buffer. A linear 20-column-volume gradient from 0% to 100 % 20 mM Tris/HCl buffer, pH 8.12, containing 0.5 M NaCl was used to the elute the protein-polymer conjugates. Fractions (2 ml) collected during ion exchange chromatography separation were analyzed by HPLC SEC as described above. A fraction containing the mono- and di-MPEG-mFc-TMP conjugates in an approximate ratio of 2.3 to 1 (as determined by SEC HPLC) was concentrated, and sterile filtered.

Example 6

In vivo Testing

[00254] BDF1 mice (Charles River Laboratories, Wilmington, Massachusetts) were divided into groups of 10 and injected on days 0, 21, and 42 subcutaneously with either diluting agent (Dulbecco's PBS with 0.1% bovine serum albumin) or diluting agent with 50 μg test mono- and di-MPEG-mFc-TMP conjugate protein (as described above) per kg animal. Each group was divided in half and bled (140 μl) from the retro-orbital sinus on alternate time points (days 0, 3, 5, 7, 10, 12, 14, 19, 24, 26, 28, 31, 33, 40, 45, 47, 49, 52 and 59). On day 59, mice were anesthetized with isoflurane prior to bleeding. The collected blood was

analyzed for a complete and differential count using an ADVIA 120 automated blood analyzer with murine software (Bayer Diagnostics, New York, NY).

Example 7

Lyophilized human Fc-TMP

[00255] Initial Lyophilized Formulation Screening Studies

The human Fc-TMP peptibody described herein in Example 7 corresponds to a dimeric form of SEQ ID NO:1017, wherein the human Fc is SEQ ID NO:1, having an initiator methionine at the N-terminus.

[00256] The stability of Fc-TMP was assessed by several chromatographic techniques: Reversed-Phase HPLC, Cation-Exchange HPLC, Size-Exclusion HPLC and SDS-PAGE, all of which were stability-indicating at elevated temperature. Formulations ranging in concentration from 0.1 to 40 mg/ml were examined for both chemical and physical degradation at accelerated, refrigerated and frozen temperature. Fc-TMP stability was evaluated with respect to varying pH and the inclusion of mannitol or glycine as cake-forming agents and sucrose as a lyoprotectant. Mannitol and sucrose were eventually chosen for further optimization after the other candidate (glycine) showed no improvement in protein stability. Tween-20 (polysorbate-20) was also shown to inhibit aggregation upon lyophilization over a concentration range of 0.002 to 0.1%. The following buffers were examined in screening studies over a pH range of 4-8: glycine, succinate, histidine, phosphate, and Tris. From these screening studies, Fc-TMP formulated in histidine buffer at pH 5 with a small amount of Tween-20 (0.004%) added was shown to be more optimal for stability.

[00257] Validation of Sucrose and Tween-20 in the Fc-TMP Formulation

[00258] Subsequent development efforts were focused on validating the level of sucrose, mannitol and Tween-20 in the formulation at a protein concentration of approximately 0.5 mg/ml (to accommodate the anticipated dosing requirements in the clinic). The effect of sucrose, mannitol and Tween-20 in optimizing stability was demonstrated in these studies. Follow-up studies were also initiated for the purpose of anticipating manufacturing issues and concerns.

[00259] Sucrose is Beneficial in Minimizing Chemical Degradation at Elevated Temperature

[00260] The effect of varying sucrose and mannitol concentrations on the stability of Fc-TMP was tested. The protein was formulated at 0.3 and 2 mg/ml in order to bracket the

anticipated concentration range in the clinic. In addition, samples were prepared with and without 0.004% Tween-20. The ratio of sucrose:mannitol was changed by varying the amount of sucrose and adjusting the mannitol level at each sucrose concentration to maintain isotonicity. The following ratios of sucrose:mannitol were examined (expressed as percent weight per volume): 0.2:5.1; 0.5:4.8; 1:4.5; 1.5:4.3 and 2:4.

[00261] Higher ratios of sucrose:mannitol are shown to minimize chemical degradation as monitored by Cation-Exchange and Reversed-Phase HPLC. As is shown in Table 39, the percent main peak is compared initially and after elevated temperature storage of Fc-TMP for 18 weeks at 37°C. The greatest loss of cation-exchange main peak occurs in the liquid formulation (Fc-TMP formulated in 10mM acetate, 5% sorbitol at pH 5), followed by the lyophilized formulations with 0.2, 0.5 and 1.0% sucrose, respectively. The protective effect of sucrose in minimizing chemical degradation was also observed by Reversed-Phase HPLC analysis of samples after elevated temperature storage (Table 39). The percent main peak (determined from reversed-phase HPLC analysis of Fc-TMP) drops significantly at the low sucrose levels, but does not appear to change meaningfully in formulations with sucrose concentrations of greater than 1%. Interpreted together, these results indicate that maintaining sucrose levels at 1.5% or higher is critical for the stability of Fc-TMP upon lyophilization.

Table 39

Fc -TMP in 10mM Histidine, buffered at pH 5 with Tween-20
Loss of RP and CEX-HPLC Main Peak After 18 Weeks at 37°C

	RP-HPLC		CEX-HPLC	
Formulation	Time Zero	18 Weeks	Time Zero	18 Weeks
0.2% Sucrose, 5.1% Mannitol	78.6	72.2	79.8	62.6
0.5% Sucrose, 4.8% Mannitol	77.3	73.1	78.9	71.6
1% Sucrose, 4.5% Mannitol	78.4	78.0	80.5	73.9
1.5% Sucrose, 4.3% Mannitol	73.2	79.8	80.5	78.7
2% Sucrose, 4% Mannitol	79.2	81.3	78.6	78.9
10mM Acetate, 5% Sorbitol, pH 5 (liquid control)	74.7	42.8	75.5	34.1

[00262] Whereas Fc-TMP in the liquid control(the 10mM acetate, 5% sorbitol, pH 5 formulation) has significant growth in the pre- and post-main peak area, the protein shows more degradation in the post-main peak region upon analysis of lyophilized samples with lower amounts of sucrose. Previous work with liquid stability samples (after elevated temperature storage) has shown that deamidation arises from glutamine and arginine in the protein, which contributes to the growth in the pre-peak region in liquid samples.

[00263] At refrigerated temperature, chemical degradation is not observed by cation-exchange and reversed-phase HPLC in the lyophilized formulation after long term storage. For example, cation-exchange chromatograms did not show apparent changes under varied temperatures (–80°C, 4°C and controlled room temperature for 6 months). Due to the lack of chemical degradation in the lyophilized formulation over time at controlled room temperature and lower, much of the formulation development work centered on minimizing the physical aggregation associated with freeze-drying.

[00264] Tween-20 Minimizes Aggregation Induced by Lyophilization

[00265] The inclusion of Tween-20 at a low concentration (0.004%) is needed to minimize a small amount of aggregation which is apparent following lyophilization. This can be demonstrated by examining the relevant results from several stability studies in which samples are evaluated for stability with and without the addition of Tween-20.

[00266] A higher protein concentration of Fc-TMP was first used to explore a wide range of Tween-20 in order to investigate the amount needed to minimize aggregation. The Fc-TMP concentration in this study was 20 mg/ml, with the Tween-20 levels set at 0.002, 0.004, 0.006 and 0.01%. After storage for one year at 4°C, aggregation is limited to <0.1% in all formulations with Tween-20. Six month results also showed no meaningful aggregation. Tween-20 at 0.004% was chosen for further consideration in the formulation studies, as discussed herein, designed for Fc-TMP at 0.5 mg/ml.

[00267] Table 40 shows the amount of aggregation in Fc-TMP monitored at time zero, 3 and 11 months after storage at 4°C. In this study, Fc-TMP was lyophilized at 0.5 mg/ml in the aforementioned formulation and in formulations with varying sucrose:mannitol ratios without Tween-20 added. In addition, stability was followed in the current formulation without Tween-20 and buffered at pH 4.5, 5 and 5.5. Results show that only the aforementioned formulation has minimal aggregation at pH 5. In formulations without Tween-20, aggregation varies from 0.5% to around 5%. Aggregation is also higher at pH 4.5 and 5.5 compared to that detected at pH 5. Lower sucrose:mannitol ratios (0.2, 0.5 and 1% sucrose formulations) have higher aggregation, as levels are typically around 5%. Over time,

the level of aggregation remains consistent in the aforementioned formulation and in the formulation without Tween-20 through the 1 year timepoint.

Table 40

Fc -TMP in 10mM Histidine, varied formulations, 0.5 mg/ml
SEC-HPLC Measured Percent Aggregation

Formulation	Time Zero	3 Months	11 Months[1]
2% Sucrose, 4% Mannitol, pH 5.0 (with 0.004% Tween-20)	<0.1	<0.1	<0.1
2% Sucrose, 4% Mannitol, pH 4.5	2.4	2.9	-
2% Sucrose, 4% Mannitol, pH 5.0	0.5	1.6	0.8
2% Sucrose, 4% Mannitol, pH 5.5	2.3	2.5	-
0.2% Sucrose, 5.1 % Mannitol, pH 5.0	4.8	7.3	-
0.5% Sucrose, 4.8 % Mannitol, pH 5.0	5.1	4.4	-
1% Sucrose, 4.5% Mannitol, pH 5.0	4.5	4.3	-

1 The optimized formulation samples were selected for evaluation at the 11 month timepoint.

[00268] Additional formulation studies were designed to confirm the beneficial effect of Tween-20 in minimizing aggregation. All of the samples in these studies were formulated at pH 5 with and without 0.004% Tween-20. Table 41 lists the percent aggregation after storage at 4°C for time intervals of zero, 18 weeks and 1 year in stability. At time zero, immediately following lyophilization, aggregation is minimized in all of the samples with 0.004% Tween-20. Small amounts of aggregation are observed in samples without Tween-20, with the highest amount found in the formulation with 0.2% sucrose. The effectiveness of Tween-20 in minimizing aggregation also extends to the 18 week timepoint, with higher percent aggregation found in samples lacking Tween-20 and at low sucrose: mannitol ratios. After storage for one year at 4°C, aggregation is also consistently low in the samples

containing Tween-20.

Table 41

Fc -TMP in 10mM Histidine, varied formulations, 0.3 mg/ml, pH 5
SEC-HPLC Measured Percent Aggregation after Storage at 4°C

Formulation	Time Zero	4 Months	1 Year [1]
2 % Sucrose, 4 % Mannitol (with 0.004% Tween-20)	<0.1	0.2	<0.1
2 % Sucrose, 4 % Mannitol	0.2	0.2	-
0.2 % Sucrose, 5.1 % Mannitol (with 0.004% Tween-20)	<0.1	<0.1	<0.1
0.2 % Sucrose, 5.1 % Mannitol	1.1	1.3	-
0.5% Sucrose, 4.8 % Mannitol (with 0.004% Tween-20)	<0.1	0.2	<0.1
0.5% Sucrose, 4.8 % Mannitol	0.2	0.8	-
1% Sucrose, 4.5% Mannitol (with 0.004% Tween-20)	<0.1	<0.1	<0.1
1 % Sucrose, 4.5% Mannitol	0.1	0.3	-
1.5 % Sucrose, 4.8% Mannitol (with 0.004% Tween-20)	<0.1	<0.1	<0.1
1.5 % Sucrose, 4.8% Mannitol	0.1	0.3	-

1 Samples with Tween-20 were selected for evaluation at the 1 year timepoint.

[00269] Another stability study, designed to test the effectiveness of antioxidants in minimizing chemical degradation, reinforced the protective effect of Tween-20. Antioxidants did not have an impact in minimizing chemical degradation upon elevated temperature storage. However, the aforementioned formulation, with 0.004% Tween-20 and at an Fc-TMP concentration of 0.2 mg/ml, had <0.1% aggregation at time zero and 0.1% after 5 months storage at 4°C. The same formulation without Tween-20 had 0.4% aggregation at time zero and 1% aggregation after storage for 5 months.

[00270] The stability study results presented in Tables II, III and the aforementioned studies illustrate the protective effect of Tween-20 in minimizing aggregation upon lyophilization. The growth of aggregation over time is minimal, as timepoints extending to 1 year at 4°C show no meaningful increases in aggregation in samples formulated with 0.004% Tween-20. Based on these stability study results which show that the addition of Tween-20 minimizes aggregation upon lyophilization, scale-up work was initiated with the recommended formulation.

[00271] **Scale-Up Studies**

[00272] Aggregation is Concentration Dependent

[00273] An initial scale-up study was designed to simulate manufacturing conditions and examine the robustness of the formulation with respect to shipping stress and stability upon reconstitution. Fc-TMP was buffer exchanged into the formulation buffer using a tangential flow filtration device, similar to larger scale processes. The protein was subsequently diluted to concentrations of 0.5 and 0.1 mg/ml with Tween-20 also added prior to the final filtration step. After samples were filled, lyophilization was performed. An

exemplary lyophilzation process is set forth below:

Thermal Treatment Steps

	Temp	Time	Ramp/Hold
Step #1	-50	120	R
Step #2	-50	120	H
Step #3	-13	60	R
Step #4	-13	360	H
Step #5	-50	60	R
Step #6	-50	60	H

Freeze Temp	-50C
Additional Freeze	0 min
Condenser Setpoint	-60 C
Vacuum Setpoint	100 mTorr

Primary Drying Steps

	temp	time	Vac	Ramp/Hold
Step #1	-50	15	100	H
Step #2	-25	120	100	R
Step #3	-25	600	100	H
Step #4	-25	600	100	H
Step #5	0	800	100	R
Step #6	25	800	100	R
Step #7	25	800	100	H
Step #8	25	800	100	H
Step #9	25	0	100	H
Step #10	25	0	100	H
Step #11	25	0	100	H
Step #12	25	0	100	H
Step #13	25	0	100	H
Step #14	25	0	100	H
Step #15	25	0	100	H
Step #16	25	0	100	H
Post Heat	25	100	100	H

Secondary Temperature 28C

[00274] Passive storage at 4°C resulted in more aggregation at the low Fc-TMP concentration (0.1mg/ml). At time zero, aggregation was determined by SEC-HPLC to be 0.4% in the 0.1 mg/ml formulation, whereas 0.1% aggregation was detected in the protein formulated at 0.5 mg/ml. After six months storage at refrigerated temperature, the aggregation remained at the same levels as observed for the time zero samples for both concentrations of Fc-TMP, in agreement with results from previous stability studies. Due to the higher amount of aggregation observed at the lowest concentration (0.1mg/ml) it was decided that 0.5 mg/ml would be best suited as the concentration of choice for additional scale-up work.

[00275] Aggregation Does Not Increase Upon Simulated Shear Stress

[00276] Lyophilized samples (not reconstituted) from the initial scale-up study were also subjected to simulated ground and air transportation with the aid of stress simulation

equipment. Briefly, the protocol as outlined in the ASTM (American Society of Testing Methods), Method # D-4728, was followed. Simulated ground and air transportation was accomplished using an Electrodynamic Vibration Table , Model S202, and a Power Amplifier, Model # TA240 (Unholtz-Dickie Corporation, Wallingford, CT). Following the transportation stress, the physical appearance of the lyophilized cakes was compared to passive controls, with the result that no morphological changes of the cake were obvious. Both chemical and physical stability was acceptable, with aggregation consistent in the stressed samples and passive controls (<0.1% in the 0.5mg/ml samples compared to 0.4% in the 0.1 mg/ml samples).

[00277] Stability upon reconstitution was examined in this study by preparing freshly reconstituted samples and incubating for 3, 7 and 14 days either passively, with slow tumbling, or vigorous shaking. Table 42 shows the results for the 0.1 and 0.5 mg/ml formulations. As is expected, the amount of aggregation is minimized in the formulations at 0.5 mg/ml. Compared to the slow tumbling over time vs. the non-tumbled samples, no meaningful increase in aggregation is apparent over the 14 day period. The amount of dimerization in these formulations (Non-tumbling and Tumbling) is also consistent. Interestingly, the shaking results appear to display a trend; i.e. the aggregation drops to less than detectable levels after time zero in both the 0.1 and 0.5 mg/ml samples. Meanwhile, there is a corresponding increase in the amount of dimerization observed in most shaken samples at each timepoint, suggesting that there is some reversibility in going from the aggregate to the dimer state upon shear stressing Fc-TMP.

Table 42

Fc -TMP in 10mM Histidine, with 2% Sucrose, 4% Mannitol and 0.004% Tween-20, pH 5
SEGHPLC Measured Percent Aggregation and Dimerization after Storage at

0.1 mg/ml	Time Zero agg, dimer	3 Days agg, dimer	7 Days agg, dimer	14 Days agg, dimer
Non-Tumbling	0.4, 0.3	1.2, 0.6	1.1, 0.4	1.0, 0.4
Tumbling	0.4, 0.3	0.7, 0.4	0.7, 0.3	1.1, 0.3
Shaking	0.4, 0.3	<0.1, 0.9	<0.1, 0.1	<0.1, 1.6
0.5 mg/ml				
Non-Tumbling	0.1, 0.5	0.2, 0.5	0.2, 0.5	0.2, 0.6
Tumbling	0.1, 0.5	0.2, 0.6	0.1, 0.6	0.1, 0.6
Shaking	0.1, 0.5	<0.1, 0.9	<0.1, 1.0	<0.1, 2.2

[00278] Secondary Drying for 12 Hours in the Lyophilization Cycle is Sufficient for Minimizing Residual Moisture

[00279] A second scale-up study was performed in which Fc-TMP was buffer-exchanged and diluted to 0.5 mg/ml in the recommended formulation. Lyophilization was achieved with a cycle consisting of an initial freezing step at -50°C, followed by annealing at -13°C. The temperature was then ramped down to -50°C, held for an hour, and primary drying initiated at -50°C with a vacuum setpoint of 100mTorr. Following a brief hold period at -50C, the temperature was ramped down to -25°C over a two hour period, maintained at -25°C for 20 hours, and then gradually raised to 25°C after around 27 hours for the beginning of secondary drying. Secondary drying was continued for a minimum of 12 hours at 25°C. During the lyophilization cycle, samples were pulled after 12, 18 and 24 hours of secondary drying in order to check the stability and compare the level of residual moisture. Results show that residual moisture, as measured by Karl Fisher Titration, is around 0.6% or less (Table 43) in all samples examined. Moisture is similarly low in the buffer placebo cakes.

Based on this work, the secondary drying time of the lyophilization cycle can be shortened to a range between 12 – 18 hours.

Table 43

Residual Moisture in Fc -TMP
Secondary Drying Times Held at 12, 18 and 24 Hours

Secondary Drying Time	Karl Fisher Percent Moisture
12 hours	0.23
12 hours	0.38
Buffer Placebo	0.43
18 hours	0.63
18 hours	0.28
Buffer Placebo	0.3
24 hours	0.46
24 hours	0.37
Buffer Placebo	0.31

[00280] Stability results are also comparable over this secondary drying time range, as samples do not have differences with respect to chemical or physical stability. For example, the amount of aggregation is <0.1% for all samples examined, while the percent dimer is consistently at 0.1%. These results confirm that the secondary drying time can be shortened to less than 24 hours without affecting the initial stability of the protein.

[00281] Additional work was performed to evaluate the robustness of the formulation with respect to varying excipient concentrations. Since previous stability work had shown that sucrose, for example, can have an impact on stability, it was necessary to examine the robustness of Fc-TMP upon minor changes in excipient levels.

[00282] **Statistical Study of Fc-TMP**

[00283] Robustness of Formulation

[00284] An initial statistical study had been designed to examine minor changes in formulation variables such as the formulation pH, histidine buffer strength and the sucrose:mannitol ratio, using an E-chip software package. These samples were lyophilized but a non-optimal freeze-dry cycle was used which resulted in higher aggregation than typically observed. The study was a screening study, assuming a linear response surface. Results of the stability assessment showed that the pH (4.7 to 5.3) and histidine buffer strength, (varied from 5 to 15 mM), had little impact on the stability of Fc-TMP. In order to verify the contribution of Tween-20 and the sucrose:mannitol ratio in the overall stability of Fc-TMP, a follow-up statistical design study was initiated using the more optimal lyophilization cycle.

[00285] Quadratic Statistical Stability Study

[00286] The second statistical design study examined variations in Tween-20 (0.001%, 0.0045% and 0.008%), the sucrose:mannitol ratio(1.7:4.2, 2:4 and 2.3:3.8), and variations in the protein concentration (0.3, 0.65 and 1mg/ml). The pH of the formulations were also adjusted to 4.7, 5 and 5.3, and the Histidine buffer strength varied from 7, 10 and 13 mM. Samples were prepared and lyophilized using a Virtis lyophilizer (SP Industries, Inc., Gardiner, NY), with an optimized conservative cycle used for the previous stability studies. Stability results were interpreted using E-chip (statistical design software package, Hockessin, DE) in two ways: an assessment of the impact of formulation variables on the amount of aggregation and dimerization observed at time zero, and the effect of formulation variables in affecting elevated temperature (37°C) storage stability as measured by rates of change from time zero.

[00287] Time Zero Formulation Results from Quadratic Statistical Study

[00288] Results from the time zero assessment showed that, as expected, Tween-20 minimizes aggregation, however the protein concentration was also significant in reducing the tendency to aggregate upon freeze-drying. The E-chip software program assesses the effects that different input variables (the formulation conditions) have on Fc-TMP aggregation and dimerization during freeze-drying. With respect to Fc-TMP dimerization at time zero, not one excipient of the formulation was considered (based on E-chip results) to have a significant effect. Several formulation variables impacted the amount of aggregation observed upon freeze-drying Fc-TMP. Based on the summary results provided by E-chip, the Fc-TMP concentration had the greatest effect on the degree of aggregation observed at time zero, followed by the Tween-20 level. Aggregation is observed to be the highest, at time zero, in the low concentration samples. Likewise, higher amounts of Tween-20 have more of

a protective effect in minimizing aggregation at time zero, although this trend is not as meaningful as the protein concentration effect. Higher amounts of aggregation were observed in this study compared to previous study results, and around 0.5% aggregation was observed in some samples at the lower protein concentrations with Tween-20.

[00289] It was observed that the variability in aggregation drops as the protein concentration increases. At 0.5 mg/ml and higher concentrations , Fc-TMP has average lower aggregation than in samples formulated at or below 0.3 mg/ml.

[00290] Tween-20 at 0.004% is Effective in Minimizing Aggregation upon Elevated Temperature Storage

[00291] The Statistical Design study was also used to assess changes upon elevated temperature storage. Rates of aggregation were compared in the varied formulation conditions after 16 days at 37°C by subtracting the elevated temperature results from the initial (time zero) results and normalizing to one month's time. Rates which are negative thus refer to an apparent loss of the measured property over time. Response variables (corresponding to results from assays) were determined through RP-HPLC (percent main-peak purity and pre-peak percent), cation-exchange HPLC (percent main-peak purity), size-exclusion HPLC (aggregation and dimer formation) and NIR-water (residual moisture by infra-red spectroscopy, which was correlated with Karl Fisher Titration results in some samples to verify accuracy).

[00292] Results from a comparison of the rates of change obtained from each assay technique show that changes in aggregation and RP-HPLC oxidation were statistically significant with respect to the Fc-TMP concentration and Tween-20 squared concentration, to within two standard deviations. The Tween-20 squared term most likely arises from the quadratic nature of the study which assumes a curved response surface. In this case, the squared Tween-20 term fits the model better, in addition to possibly suggesting that there is an interactive effect with itself which affects stability. The other measured responses, such as cation-exchange HPLC main-peak purity, or the varied pH conditions, for example, did not exhibit any significant responses in affecting protein stability.

[00293] As is the case with the initial scale-up study previously discussed (tumbled, non-tumbled and shaken samples), the amount of aggregation is lower after high temperature storage. The rate of change in these samples was used to make predictions based on the statistical model (quadratic study) to anticipate the protective effect of Tween-20. Table 44 shows predictions for the amount of aggregation expected, based on the statistical design model, as the Tween-20 concentration is raised from 0 to 0.008%. As is shown, the rate of

aggregation, normalized to one month at 37°C, is negative (indicating the loss of aggregate in these conditions) with the exception of 0% Tween-20, in which case aggregation would be predicted to grow. The rate of loss of aggregate appears to plateau at Tween-20 concentrations of 0.002% and higher, suggesting that Tween-20 at low levels (0.002-0.006%) is sufficient in minimizing physical degradation. The rate of growth of dimer is correspondingly similar under these conditions and was not statistically correlated with any of the formulation excipients, as previously mentioned.

Table 44

Statistical Quadratic Model Predictions
Varied Tween-20 and Fc -TMP Concentration
Based on 16 Days Incubation at 37°C (normalized to one month)

% Tween 20	Fc-TMP (mg/ml)	% SEC Aggregation	prediction limits	% RP-HPLC Oxidation	prediction limits
0	0.5	0.09	(-0.32, 0.50)	0.47	(-2.59, 1.65)
0.002	0.5	-0.35	(-0.69, -0.0)	-0.68	(-2.44, 1.08)
0.004	0.5	-0.53	(-0.87, -0.19)	-0.58	(-2.32, 1.17)
0.006	0.5	-0.45	(-0.78, -0.12)	-0.17	(-1.86, 1.52)
0.008	0.5	-0.12	(-0.46, 0.21)	0.54	(-1.18, 2.26)
0.004	0.3	-0.59	(-0.94, -0.25)	0.58	(-1.18, 2.34)
0.004	0.1	-0.63	(-1.10, -0.16)	2.69	(0.28, 5.09)

[00294] The rate of change in RP-HPLC measured oxidation at 0.5 mg/ml, assuming that this corresponds to changes in the pre-peak region of each chromatogram, is not statistically significant with respect to the Tween-20 squared term. In this case, the model (as shown in Table 44) predicts that as the Tween-20 concentration is varied the rate of oxidation is consistent with the limits of the prediction intervals. The protein concentration affects oxidation, as the rate of growth increases from 0.58 to 2.69 as the protein concentration drops from 0.3 to 0.1 mg/ml (while keeping the Tween-20 constant at 0.004%.).

[00295] These results suggest that maintaining the Tween-20 concentration between 0.002 to 0.006% is desirable from a stability standpoint. The amount of protein is also important, as the stability is worse at concentrations below 0.5 mg/ml.

[00296] Refrigerated Temperature Stability

[00297] Considering the above, the following formulation was used for assessing the refrigerated temperature stability of lyophilized Fc-TMP: 0.5 mg/ml Fc-TMP in 10mM Histidine buffered at pH 5, 2% Sucrose, 4% Mannitol, and 0.004% Tween-20.

[00298] The formulation was monitored for refrigerated temperature stability for a period of one year. Table 45 shows the stability results from this study, with results from time zero, 3 months and 1 year listed. As is shown, the percent main peak purity, as measured by Reversed-Phase and Cation-Exchange HPLC, does not appear to decrease with time. The minor differences in main-peak purity over time are typical of the normal variation in resolution of the chromatographic columns and are also observed in the frozen standard. The percent aggregation is consistent and does not appear to grow after one year.

Table 45

Reversed-Phase HPLC Percent Main Peak

Concentration	Timepoint 0	3 months	1 Year
0.3	81.0	82.5	82.4
0.5	69.0	82.7	83.4
1.0	80.6	82.4	83.2
Frozen Starting Material	82.4	84.0	84.5

Cation-Exchange HPLC Percent Main Peak

Concentration	Timepoint 0	3 months	1 Year
0.3	67.0	71.8	81.8
0.5	73.5	83.1	80.0
1.0	74.2	79.7	80.5
Frozen Starting Material	75.3	77.0	83.6

Size-Exclusion HPLC Percent Aggregation

Concentration	Timepoint 0	3 months	1 Year
0.3	<0.1	0.1	0.1
0.5	<0.1	<0.1	0.1
1.0	<0.1	<0.1	<0.1
Frozen Starting Material	0.1	0.1	<0.1

[00299] Fc-TMP is formulated in 10mM Histidine, buffered at pH 5.0 with 2% sucrose, 4% mannitol and 0.004% Tween-20. It has been shown that pH 5 is more optimal for stability, and that the sucrose: mannitol ratio is critical in minimizing chemical degradation upon storage at elevated temperature for this protein system. Tween-20 is needed at a low concentration in order to minimize the amount of aggregation which occurs

as a result of the lyophilization process. Stability studies for scale-up applications support these conclusions. Statistical studies have also been designed which validate the level of each excipient in the formulation, including the need for the protein concentration to be at 0.5 mg/ml. Refrigerated temperature stability of the recommended formulation does not show meaningful degradation after storage for one year at 4°C.

Example 8

Lyophilized Fc-Ang-2 binding peptide

[00300] In order to determine the optimal formulation for lyophilized Fc-Ang-2 binding peptide, analyses were carried out that assessed Fc-Ang-2 binding peptide aggregation and stability at various pH values, excipient concentrations, and protein concentrations.

[00301] Fc-Ang-2 binding peptide consists of two pharmaceutically active polypeptide molecules linked to the C-terminus of the Fc portion of an IgG1 antibody molecule. The molecule is comprised of 574 amino acid residues with a total molecular weight of 63,511 Daltons. The pI of the molecule is 5.45. There are two disulfide bonds on each of the active polypeptides. There are a total of 20 cysteine residues throughout the molecule, most of which are oxidized in disulfide bridges. The sequence of Fc-Ang-2 binding peptide is as follows:

MDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLS
PGKGGGGGAQQEECEWDPWTCEHMGSGSATGGSGSTASSGSGSATHQEECEWDPW
TCEHMLE (SEQ ID NO: 2)

[00302] The Fc portion of the IgG1 terminates at K228. G229-G233 composes a linker sequence. The active polypeptide begins at A234 and extends to the rest of the sequence.

[00303] Lyophilized Fc-Ang-2 binding peptide pH screen

[00304] The pH screen tested the stability of an Fc-Ang-2 binding peptide at pH 4.0, 7.0, and 8.0. At pH 4.0, the screened buffers included glutamic acid, sodium citrate, and sodium succinate, each at a concentration of 10 mM. At pH 7.0, the screened buffers were histidine and tris, both at 10 mM concentration. Hisitidine and Tris were also screened at pH 8.0, each at 10 mM. Each of the buffers contained 4% mannitol as a lyophilization caking

agent and 2% sucrose as an excipient. In addition, the histidine buffer at pH 7.0 was examined with and without the presence of a surfactant, 0.01% Tween 20 (w/w). The protein was diluted to 5 mg/ml with each of the formulation buffers. This solution was then dialyzed into each of the formulation buffers using dialysis tubing with a 10,000 Da molecular weight exclusion limit, where a total of 6 exchanges were performed with a minimum of 4 hours of equilibration between exchanges. After dialysis, the protein was aliquoted into 3 cc glass vials with a 1 ml fill volume. These vials were then lyophilized using a lab-scale freeze-drying instrument. After lyophilization, the vials were sealed and stored for incubation at 4°C, 29°C, and 37°C, where individual vials were pulled and analyzed at various points over time, beginning immediately after lyophilization and extending out to a period of 24 months. The samples were reconstituted with the appropriate volume of water and analyzed for protein stability using size exclusion liquid chromatography and gel electrophoresis (which detect aggregation, dimerization and proteolytic cleavage), anion exchange liquid chromatography (which detects oxidation). In addition, the properties of the cake such as reconstitution times and moisture and properties of the reconstituted liquid solution were analyzed (such as pH).

[00305] Lyophilized Fc-Ang-2 binding peptide Excipient Study

[00306] The excipient screen was performed in a single buffer, 10 mM hisitidine at pH 7.0. The two excipients compared in this study were 0.85% arginine and 1% sucrose. The caking agent used with arginine was 4% mannitol, and the caking agent used with sucrose was 2% glycine. Each of the formulations was tested at protein concentrations of 1 mg/ml, 30 mg/ml, and 60 mg/ml. In addition, one formulation containing a manntiol sucrose combination was tested at 30 mg/ml. Each of the formulations contained 0.01% Tween 20. The protein was first concentrated to 70 mg/ml and dialyzed into the appropriate formulation using a lab-scale ultrafiltration/diafiltration device. The protein was then diluted to each of the three concentrations with the appropriate formulation buffer. The protein was then aliquoted into 3 cc glass vials with a fill volume of 1 ml. The vials were then lyophilized using a lab-scale freeze-drying instrument. After lyophilization, the vials were sealed and stored for incubation at 4°C, 29°C, 37°C, and 52°C, where individual vials were pulled and analyzed at various points over time, beginning immediately after lyophilization and extending out to a period of 24 months. The samples were analyzed for protein stability using size exclusion chromatography, anion exchange chromatography and SDS-PAGE. The properties of the lyophilized cake and reconstituted liquid solutions were also analyzed.

[00307] Lyophilized Fc-Ang-2 binding peptide Concentration Screen

[00308] The concentration screen was performed in 10 mM histidine at pH 7.2, with 4% mannitol as the caking agent and 2% sucrose as an excipient. The protein was concentrated to approximately 140 mg/ml and dialyzed into the formulation using a lab-scale ultrafiltration/diafiltration device. The dialyzed protein was then diluted to 30 mg/ml, 60 mg/ml, and 120 mg/ml in the formulation buffer. The solutions were then aliquoted into 3 cc glass vials at a fill volume of 1 ml. The vials were lyophilized using a lab-scale freeze-drying instrument. After lyophilization, the vials were sealed and stored for incubation at 4°C, 29°C, 37°C, and 52°C, where individual vials were pulled and analyzed at various points over time, beginning immediately after lyophilization and extending out to a period of 24 months. The samples were analyzed for protein stability using size exclusion chromatography, anion exchange chromatography and SDS-PAGE. The properties of the lyophilized cake and reconstituted liquid solutions were also analyzed.

[00309] Conclusion

[00310] Considering the above, the optimal formulation(s) comprises 10 mM histidine, 4% mannitol, 2% sucrose, 0.01% Tween-20, pH 7.0.

Example 9

Lyophilized Fc-Agp-3 binding peptide

[00311] In order to determine the optimal formulation for lyophilized Fc-Agp-3 binding peptide, analyses were carried out that assessed Fc-Agp-3 binding peptide aggregation and stability at various pH values, excipient concentrations, and protein concentrations.

[00312] Fc-Agp-3 binding peptide is a N-linked peptibody against the B cell activation factor (BAFF) aimed against B cell-related diseases. The peptibody is constructed of two non-glycosylated disulfide-linked polypeptides with a total mass of ~63.6 kD. The isoelectric point for this peptibody has been estimated to be pH 7.36.

[00313] Fc SEQUENCE (SEQ ID NO: 1696):

VDKTHTCPPCPAPELLGGPSVFLFPPKP KDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQ
PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC
SVMHEALHNHYTQKSLSLSPGK

[00314] Agp-3 BINDING PEPTIDE SEQUENCE (SEQ ID NO: 1697):

GCKWDLLIKQWVCDPLGSGSATGGSGSTASSGSGSATHMLP GCKWDLLIKQWVCDPLGGGGG

[00315] Thus, the sequence of Fc-Agp-3 binding peptide binding peptide is as follows:

GCKWDLLIKQWVCDPLGSGSATGGSGSTASSGSGSATHMLP GCKWDLLIKQWVCDPLGGGGGGVDKTHTCPPCPAPELLGGPS VFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK (SEQ ID NO: 1698)

[00316] Lyophilized Fc-Agp-3 binding peptide broad pH Screen at 10 mg/ml

[00317] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating at elevated temperatures. To assess the stability and reconstitution properties of lyophilized Fc-Agp-3 binding peptide over the pH range of 3.85-7.6, 10mg/mL Fc-Agp-3 binding peptide was formulated in various 10 mM buffers in the presence of 2.5% mannitol and 2.0% sucrose. The following buffers were tested at approximately 0.5 pH unit increments: acetate, succinate, histidine, pyrophosphate, phosphate and Tris.

[00318] For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was dialyzed into the appropriate formulation buffers and lyophilized in a Virtis lyophilizer using a conservative cycle. The annealing step was performed at -20°C and lasted for 4 hours to allow for mannitol crystallization. The primary drying was performed at the shelf temperature of -25°C for 20 hours. The primary drying reached completion at -25°C since no spike in the vacuum was observed as the shelf temperature was increased up to 0°C. No major collapse was observed and the samples proceeded successfully through the secondary drying first at 0°C, and then at 25°C. Upon reconstitution the formulations with pH at or above 7 were slightly turbid, while all the other formulations were clear. This was explained by the proximity of the high pH formulations to the isoelectric point of Fc-Agp-3 binding peptide (pI=7.36). SE-HPLC analysis revealed a dimer as the main high molecular weight specie. It was observed that relative % dimer was strongly pH dependent with the lowest accumulation at pH 5 and below. The amount of soluble aggregates also showed some pH dependence. No soluble

aggregates were observed in the samples prior to lyophilization. In contrast, a small amount of dimer was present in all formulations prior to lyophilization, and it increased further in the reconstituted samples, post lyophilization. No significant clipping was observed in all formulations. The highest amount of the intact monomer was in the case of acetate, succinate and histidine formulations at pH 5 and below.

[00319] Lyophilized Fc- Agp-3 binding peptide broad pH Screen at 30 mg/ml: stabilizing effect of sucrose and mannitol

[00320] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating. To evaluate the effect of the presence of 2.5% mannitol and 3.5% sucrose on stability and reconstitution properties of lyophilized Fc-Agp-3 binding peptide over the pH range of 4.5—7.5, Fc-Agp-3 binding peptide was formulated at 30mg/mL in 10 mM succinate, histidine and phosphate buffers. Pyrophosphate and Tris buffers were excluded from this study due to poor performance in the previous broad pH screen. Acetate buffer was excluded due to possibility of pH changes in the reconstituted samples as a result of acetate sublimation during freeze-drying.

[00321] For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was dialyzed into the appropriate formulation buffers and lyophilized in a Virtis lyophilizer using a conservative cycle. The annealing step was performed at -20°C and lasted for 5 hours to allow for more complete mannitol crystallization. The primary drying was performed at the shelf temperature of -25°C for 20 hours. The primary drying not quite reached completion at -25°C, and some spike in the vacuum was observed as the shelf temperature was increased up to 0°C. No major collapse was observed and the samples proceeded successfully through the secondary drying first at 0°C, and then at 25°C. Upon reconstitution formulations with pH around 7 were slightly turbid, while all other formulations were clear. As it was mentioned previously, this could be explained by the proximity of the high pH formulations to the isoelectric point of Fc-Agp-3 binding peptide. SE-HPLC analysis revealed dimer as the main high molecular weight specie. Again, it was observed that relative % dimer was strongly pH dependent with the lowest accumulation at pH 5 and below. The amount of soluble aggregates did not show clear pH dependence. No soluble aggregates were observed in the samples prior to lyophilization. ~0.6% dimer was observed in the non-GMP bulk prior to formulating and it increased up to 3.0% for high pH formulations prior to lyophilization as a result of buffer exchange/concentration.

[00322] The pH dependence of the dimer accumulation was also confirmed by close correspondence of the relative amount dimer at a given pH irrespective of the type of buffer. % dimer did not increase significantly post-lyophilization as evidenced by T=0 samples. The only exception were the samples non-containing both, sucrose and mannitol, which showed noticeable, ~0.25-0.5% increase in % dimer. In the presence of sucrose the main peak loss was minimal even after buffer exchange/lyophilization for succinate and histidine formulations with pH 4.1 and 4.7, respectively. Compared to them, all phosphate formulations showed ~3% loss of the main peak prior to lyophilization. Although, the cake was formed even in the absence of both sucrose and mannitol, the corresponding main peak dropped by 0.5—0.7% compared to the sugar-containing formulations. In addition, reconstitution of the non-sugar formulations was much longer (>2 min) and required some agitation. In order to ensure robustness of the cake mannitol or glycine were included as bulking agents in all subsequent formulations even though sucrose alone was shown to confer sufficient protein stability.

[00323] Lyophilized Fc- Agp-3 binding peptide narrow pH Screen at 30 mg/ml

[00324] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC) and reversed-phase HPLC (RP-HPLC), which were stability-indicating at elevated temperatures. Since % recovery of the main peak was higher at pH 5 and below, the phosphate buffer was omitted from the narrow pH screen. In addition to the succinate and histidine buffers, which performed well in the broad pH screens, the narrow pH screen included 10 mM glutamate, pH 4—6. The formulations were tested at 0.2 pH unit increments. The sucrose and mannitol content was kept constant at 3.5% and 2.5%, respectively, except for two succinate formulations at pH 4.5 with 2.0% and 5.0% sucrose. Also, six potential generic lyo formulations were tested at every pH unit increments, such as:

[00325] 1) 20 mM histidine, 2.0% glycine, 1.0% sucrose at pH 5.0

[00326] 2) 20 mM histidine, 2.0% glycine, 1.0% sucrose at pH 6.0

[00327] 3) 20 mM histidine, 2.0% glycine, 1.0% sucrose at pH 7.0

[00328] 4) 20 mM histidine, 4.0% mannitol, 2.0% sucrose at pH 5.0

[00329] 5) 20 mM histidine, 4.0% mannitol, 2.0% sucrose at pH 6.0

[00330] 6) 20 mM histidine, 4.0% mannitol, 2.0% sucrose at pH 7.0

[00331] For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was dialyzed into the appropriate formulation buffers and lyophilized in a Virtis lyophilizer using a conservative cycle. The lyophilization cycle was futher modified. The annealing step was performed at -15°C to

allow for glycine crystallization and lasted for 5 hours. The primary drying was performed initially at -30°C for a short period of time (4 h). Then the shelf temperature was raised to -25°C and kept constant for 24 hours. However, primary drying did not quite reach completion at -25°C as evidenced by a small spike in the vacuum as the shelf temperature was further increased up to 0°C. Nevertheless, no major collapse was observed and the samples proceeded successfully through the secondary drying first at 0°C, and then at 25°C. Up to 6 months lyophilized state stability data was generated at 37°C to assess long-term stability of Fc-Agp-3 binding peptide. Increase in pH results in the loss of the main peak for all histidine formulations. Only generic formulations were monitored up to 6 months, but the advantage of the pH near 5.0 was already obvious for the 1- and 3-month timepoints. Moreover, 6-month data for the generic formulations suggests that mannitol+sucrose formulations are more stable than glycine+sucrose, especially at pH 6 and higher.

[00332] In the case of glutamate and succinate formulations there was also a clear pH-dependent increase in the amount of dimer, the main degradation product, as pH becomes less acidic. Similar pH dependence is seen for the aggregates. The highest recovery of the main peak was observed for pH 5 and below. Initial loss of the main peak for T=0 can be explained by protein degradation during buffer exchange and concentrating as evidenced by a similar loss for the formulations prior to lyophilization. However, 3-month stability data suggest that glutamate formulations had higher physical stability than their succinate counterparts (with the same pH). It has to be noted that in this study we also tested effect of increased sucrose concentrations on the stability of succinate formulations. In addition to 3.5% sucrose, we compared 2.0% and 5.0% sucrose formulations in succinate, pH 4.5. The increase in sucrose decreased high molecular weight species to some extent, but it did not significantly affect the amount of the main peak. Therefore, 3.5% sucrose was considered optimal since such formulations most closely matched with physiological tonicity.

[00333] One of clip specie was observed growing at low pH by RP-HPLC. A significant portion of the pH-dependent clipping in the lyophilized formulations occurred prior to lyophilization as a result of time-consuming buffer exchange and protein concentrating steps. After lyophilization no significant increase in the amount of clips was observed even after 3- to 6-month storage at 37°C. In general the data suggests using higher pH formulations to mitigate the clipping since it is unobservable at pH 6 and above. However, the amount of the dimer is significant at higher pH and may be as high as 2.5—4.5% at pH 6 and above. Therefore, a compromise can be found in formulating Fc-Agp-

3 binding peptide at pH 5, where clipping is moderate, especially in the glutamate and histidine buffers, and when the dimer formation is still sufficiently suppressed.

[00334] Conclusion

[00335] 2.5% mannitol and 3.5% sucrose have provided sufficient cake and protein stability as confirmed by 6-month shelf study at 37°C. Therefore, 10 mM histidine, 2.5% mannitol, 3.5% sucrose at pH 5.0 and 10 mM glutamate, 2.5% mannitol, 3.5% sucrose at pH 5.0 can be used for formulating 30 mg/mL Fc-Agp-3 binding peptide. In addition, this study shows that 20 mM histidine, 4.0% mannitol, 2.0% sucrose at pH 5.0 also performs well and can be considered as a possible generic lyo formulation for peptibodies.

Example 10

Lyophilized Fc-Myo binding peptide

[00336] In order to determine the optimal formulation for lyophilized Fc-Myo binding peptide, analyses were carried out that assessed Fc-Myo binding peptide aggregation and stability at various pH values, excipient concentrations, and protein concentrations.

[00337] Fc-Myo binding peptide is a C-linked peptibody against the myostatin protein aimed against muscle wasting-related diseases. The peptibody is constructed of two non-glycosylated disulfide-linked polypeptides with a total mass of ~59.1 kD. The isoelectric point for this peptibody has been estimated to be pH 6.88.

[00338] Fc SEQUENCE (SEQ ID NO:1699):

M D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R D E L T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

[00339] MYOSTATIN BINDING PEPTIDE SEQUENCE (SEQ ID NO:1700):

G G G G G A Q L A D H G Q C I R W P W M C P P E G W E

[00340] Thus, the sequence of Fc-Myo binding peptide binding peptide is as follows:

M D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R E P Q V Y T L P P S R D E L T K N Q V S L T C L V K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q Q G N V F S C

S V M H E A L H N H Y T Q K S L S L S P G K G G G G G A Q L A D H G Q C I R W P W M C P P E G W E (SEQ ID NO:1701)

[00341] Determination of pH condition for lyophilized Fc-Myo binding peptide

[00342] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating at elevated temperatures. A pH screen study was designed and performed to determine the optimal formulation pH in the liquid state prior to the lyophilization. Protein was formulated in pH 4.5, 4.75, 5.0, 5.5 and 6.0 with buffer agents of acetate and histidine and sucrose as the stabilizer (or lyo protectant). The formulated vials were stored at 29C for up to 1 year. Stability was monitored using SE-HPLC. The aggregation rate constants were calculated for each of the formulation conditions. The aggregation rate at pH 4.5 was found to be the minimum, therefore pH 4.5 was selected as the preferred formulation pH condition.

[00343] Lyophilized Fc-Myo binding peptide buffer agent study at 30 mg/mL.

The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating. A 30 mg/mL dosage form as investigated using three different buffering agent: 10 mM glutamate, 10 mM histidine and 10 mM succinate at pH 4.5. All formulations contain 0.004% polysorbate 20.

For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was dialyzed into the appropriate formulation buffers and lyophilized in a Virtis lyophilizer using a conservative cycle. Lyophilized protein formulation displayed acceptable cake elegance. Upon reconstitution formulations were clear Lyophilized Fc-Myo binding peptide was stored at 4, 29, 37 and 52°C. The real time stability studies were carried out at 4°C and found to be comparable for these formulations for up to 3 months. However at 52°C storage 3 months, the histidine containing formulation was slightly better than the glutamate containing formulation. The succinate containing formulation was significantly less stable than the other two formulations. Based on these results, histidine and glutamate were considered as the preferred buffer agents for the final Fc-Myo binding peptide formulation.

[00344] Lyophilized Fc-Myo binding peptide Excipient Study at 30 mg/ml: stabilizing effect of sucrose, trehalose and hydroxyethyl starch

[00345] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating. To evaluate the effect of the presence of trehalose, hydroxyethyl starch and sucrose on stability of lyophilized Fc-Myo binding peptide, Fc-Myo

binding peptide was formulated at 30mg/mL in 10 mM glutamate buffer with 4% mannitol. The concentration of trehalose and sucrose used was 2.0%, 1% hydroxyethyl starch was added to the sucrose formulation to make a final formulation of 10 mM glutamate, 4% mannitol, 2% sucrose, 1% hydroxyethyl starch. All formulations contain 0.004% polysorbate 20.

[00346] For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was dialyzed into the appropriate formulation buffers and lyophilized in a Virtis lyophilizer using a conservative cycle. Lyophilized protein formulation displayed acceptable cake elegance. Upon reconstitution formulations were clear.

[00347] The stability of these formulations was monitored using SE-HPLC.

[00348] Lyophilized Fc-Myo binding peptide was stored at 4, 29, 37 and 52°C. The real time shelf time condition stability (4°C) was found comparable between these formulations for up to 3 months. However under 52°C storage condition for 3 months, the sucrose containing formulation was slightly better than the trehalose containing formulation. Addition of hydroxyethyl starch did not display any negative impact on the stability. Based on these results, sucrose was considered as the preferred stabilizer for the final Fc-Myo binding peptide formulation.

[00349] Lyophilized Fc-Myo binding peptide Excipient Study at 30 mg/ml: stabilizing effect of sucrose and mannitol

[00350] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating. To evaluate the effect of the presence of variable amount of mannitol and sucrose on stability and reconstitution properties of lyophilized Fc-Myo binding peptide over the mannitol range of 4.0 to 8% and the sucrose range of 1.0% to 4.0%, Fc-Myo binding peptide was formulated at 30mg/mL in 10 mM glutamate buffer. All formulations contain 0.004% polysorbate 20.

[00351] For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was dialyzed into the appropriate formulation buffers and lyophilized in a Virtis lyophilizer using a conservative cycle. Lyophilized protein formulation displayed acceptable cake elegance. Upon reconstitution formulations were clear.

[00352] The stability of these formulations was monitored using SE-HPLC method. Lyophilized Fc-Myo binding peptide was stored at 4, 29, 37 and 52°C. The real time shelf

time condition stability (4°C) was found comparable between these formulations for up to 3 months. However when stored at 52°C for 3 months, an increasing amount of sucrose was found contributing to the increase in stability against aggregation. Due to a concern to maintain the isotonic condition for the final formulation which limits the total amount of disaccharides and to maintain a proper ratio of mannitol and sucrose to preserve the lyophilized cake property, 4.0% mannitol and 2.0% sucrose were the preferred excipients for the final formulation.

[00353] Lyophilized Fc-Myo binding peptide Excipient Study at 1, 30, 85 mg/mL

[00354] The stability was assessed primarily by size-exclusion HPLC (SE-HPLC), which was stability-indicating. To evaluate the effect of the protein concentration on stability and reconstitution properties of lyophilized Fc-Myo binding peptide, Fc-Myo binding peptide was formulated at 1, 30, 85 mg/mL in 10 mM glutamate buffer with 4% mannitol and 2% sucrose. All formulations contain 0.004% polysorbate 20.

[00355] For the formulation development work, purified bulk material was obtained in the 30 mg/mL frozen liquid formulation. The material was buffer exchanged into the appropriate formulation buffers using UF/DF and lyophilized in a Virtis lyophilizer using a conservative cycle. Lyophilized protein formulation displayed acceptable cake elegance. Upon reconstitution formulations were clear.

[00356] The stability of these formulations was monitored using SE-HPLC method. Lyophilized Fc-Myo binding peptide was stored at 4, 29, 37°C. The real time shelf time condition stability (4°C) was found comparable between these formulations for up to 6 months. The stability is likely acceptable for all the concentrations studied as the commercial product formulation.

[00357] Conclusion

[00358] 4.0% mannitol and 2.0% sucrose have provided sufficient cake and protein stability as confirmed by 12-month shelf study at 4°C. Therefore, 10 mM histidine, 4.0% mannitol, 2.0% sucrose at pH 4.5 and 10 mM glutamate, 4.0% mannitol, 2.0% sucrose at pH 4.5 can be used for formulating 1 to 100 mg/mL Fc-Myo binding peptide.

[00359] The present invention has been described in terms of particular embodiments found or proposed to comprise preferred modes for the practice of then invention. It will be appreciated by those of ordinary skill in the art that, in light of the present disclosure, numerous modifications and changes can be made in the particular embodiments exemplified without departing from the intended scope of the invention.

What is claimed is:

1. A lyophilized therapeutic peptibody composition comprising a buffer, a bulking agent, a stabilizing agent, and optionally a surfactant;

wherein said buffer is comprised of a pH buffering agent in a range of about 5 mM to about 20 mM and wherein the pH is in a range of about 3.0 to about 8.0;

wherein said bulking agent is at a concentration of about 0% to about 4.5% w/v;

wherein said stabilizing agent is at a concentration of about 0.1% to about 20% w/v;

wherein said surfactant is at a concentration of about 0.004% to about 0.4% w/v; and

wherein said therapeutic peptibody comprises a structure set out in Formula I,

Formula I: $[(X^1)_a\text{-}F^1\text{-}(X^2)_b]\text{-}(L^1)_c\text{-}WSP_d$

wherein:

F^1 is an Fc domain;

X^1 is selected from

$P^1\text{-}(L^2)_e\text{-}$

$P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$

$P^3\text{-}(L^4)_g\text{-}P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$ and

$P^4\text{-}(L^5)_h\text{-}P^3\text{-}(L^4)_g\text{-}P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$

X^2 is selected from:

$\text{-}(L^2)_e\text{-}P^1$,

$\text{-}(L^2)_e\text{-}P^1\text{-}(L^3)_f\text{-}P^2$,

$\text{-}(L^2)_e\text{-}P^1\text{-}(L^3)_f\text{-}P^2\text{-}(L^4)_g\text{-}P^3$, and

$\text{-}(L^2)_e\text{-}P^1\text{-}(L^3)_f\text{-}P^2\text{-}(L^4)_g\text{-}P^3\text{-}(L^5)_h\text{-}P^4$

wherein P^1, P^2, P^3, and P^4 are each independently sequences of pharmacologically active peptides;

L^1, L^2, L^3, L^4, and L^5 are each independently linkers;

a, b, c, e, f, g, and h are each independently 0 or 1,

provided that at least one of a and b is 1;

d is 0, 1, or greater than 1; and

WSP is a water soluble polymer, the attachment of which is effected at any reactive moiety in F^1.

2. The composition of claim 1 wherein said therapeutic peptibody comprises a structure set out in Formula II

Formula II: $[X^1\text{-}F^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the C-terminus of X^1, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

3. The composition of claim 1 wherein said therapeutic peptibody comprises a structure set out in Formula III

Formula III: $[F^1\text{-}X^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of X^2, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

4. The composition of claim 1 wherein said therapeutic peptibody comprises a structure set out in Formula IV

Formula IV: $[F^1\text{-}(L^1)_e\text{-}P^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $\text{-}(L^1)_e\text{-}P^1$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

5. The composition of claim 1 wherein said therapeutic peptibody comprises a structure set out in Formula V

Formula V: $[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}P^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $\text{-}L^1\text{-}P^1\text{-}L^2\text{-}P^2$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

6. The composition of any one of claims 1 through 5 wherein said therapeutic peptibody is a multimer.

7. The composition of claim 6 wherein said therapeutic peptibody is a dimer.

8. The composition of any one of claims 1 through 7 wherein P^1, P^2, P^3 and/or P^4 are independently selected from a peptide set out in any one of Tables 4 through 38.

9. The composition of claim 8 wherein P^1, P^2, P^3 and/or P^4 have the same amino acid sequence.

10. The composition of any one of claims 1 through 7 wherein the Fc domain is set out in SEQ ID NO:1.

11. The composition of any one of claims 1 through 7 wherein WSP is PEG.

12. The composition of any one of claims 1 through 7 wherein the Fc domain is set out in SEQ ID NO:1 and WSP is PEG.

13. The composition of claim 12 wherein PEG has a molecular weight of between about 2 kDa and 100 kDa.

14. The composition of claim 13 wherein said PEG has a molecular weight of between about 6 kDa and 25 kDa.

15. The composition of claim 11, wherein said composition comprises at least 50% PEGylated therapeutic peptibody.

16. The composition of claim 15 comprising at least 75% PEGylated therapeutic peptibody.

17. The composition of claim 15 comprising at least 85% PEGylated therapeutic peptibody.

18. The composition of claim 15 comprising at least 90% PEGylated therapeutic peptibody.

19. The composition of claim 15 comprising at least 95% PEGylated therapeutic peptibody.

20. The composition of any one of claims 1-19 wherein said pH buffering agent is selected from the group consisting of glycine, histidine, glutamate, succinate, phosphate, acetate, and aspartate.

21. The composition of any one of claims 1-19 wherein said bulking agent selected from the group consisting of mannitol, glycine, sucrose, dextran, polyvinylpyrolidone, carboxymethylcellulose, lactose, sorbitol, trehalose, or xylitol.

22. The composition of any one of claims 1-19 wherein said stabilizing agent selected from the group consisting of sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCL, poly-hydroxy compounds, including polysaccharides such as dextran, starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride.

23. The composition of any one of claims 1-19 wherein said surfactant selected from the group consisting of sodium lauryl sulfate, dioctyl sodium sulfosuccinate, dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, glycodeoxycholic acid sodium salt, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, hexadecyltrimethylammonium bromide, CHAPS, CHAPSO, SB3-10, SB3-12, digitonin, Triton X-100, Triton X-114, , lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 20, 40, 60, 65 and 80, soy lecithin, DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose.

24. The composition of any one of claims 1-19 wherein the therapeutic peptibody concentration is between about 0.25 mg/mL and 250 mg/mL.

25. The composition of any one of claims 1-19 wherein said pH buffering agent is 10 mM histidine and wherein the pH is 5.0;

wherein said bulking agent is 4% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.004% w/v polysorbate-20.

26. The composition of claim 25 wherein P^1 comprises a sequence set forth in Table 6.

27. The composition of claim 26 wherein the therapeutic peptibody concentration is 0.5 mg/mL.

28. The composition of any one of claims 1-19 wherein said pH buffering agent is 10 mM histidine and wherein the pH is 7.0;

wherein said bulking agent is 4% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.01% w/v polysorbate-20.

29. The composition of claim 28 wherein P^1 comprises a sequence set forth in Table 32.

30. The composition of claim 29 wherein the therapeutic peptibody concentration is 30 mg/mL.

31. The composition of any one of claims 1-19 wherein said pH buffering agent is 20 mM histidine and wherein the pH is 5.0;

wherein said bulking agent is 3.3% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.01% w/v polysorbate-20.

32. The composition of claim 31 wherein P^1 comprises a sequence set forth in Table 4.

33. The composition of claim 32 wherein the therapeutic peptibody concentration is 100 mg/mL.

34. The composition of any one of claims 1-19 wherein said pH buffering agent is 10 mM histidine and wherein the pH is 5.0;

wherein said bulking agent is 2.5% w/v mannitol and

wherein said stabilizing agent is 3.5% w/v sucrose.

35. The composition of claim 34 wherein P^1 comprises a sequence set forth in Table 31.

36. The composition of claim 35 wherein the therapeutic peptibody concentration is 30 mg/mL.

37. The composition of any of claims 1-19 wherein the composition is selected from the group consisting of:

a) 10 mM histidine, pH 4.7, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20;

b) 10 mM histidine, pH 5, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20;

c) 10 mM glutamate, pH 4.5, 4% mannitol and 2% sucrose with and without 0.004% polysorbate-20;

d) 10 mM succinate, pH 4.5, 4% mannitol and 2% sucrose, 0.004% polysorbate-20;

e) 10 mM glutamate, pH 4.5, 9% sucrose, 0.004% polysorbate-20;

f) 10 mM glutamate, pH 4.5, 4% mannitol, 2% sucrose, 1% hydroxyethyl starch, 0.004% polysorbate-20;

g) 5 mM glutamate, pH 4.5, 2% mannitol, 1% sucrose, 0.004% polysorbate-20; and

h) 10 mM glutamate, pH 4.5, 4% mannitol, 2% trehalose, 0.004% polysorbate-20.

38. The composition according to claim 37 wherein P^1 comprises a sequence set forth in Tables 21-24.

39. The composition of claim 38 wherein the therapeutic peptibody concentration is selected from the group consisting of 1, 30, 85, and 100 mg/mL.

40. A method for making a lyophilized therapeutic peptibody comprising the steps of:

a) preparing a solution of a buffer, a bulking agent, a stabilizing agent, and optionally a surfactant;

wherein said buffer is comprised of a pH buffering agent in a range of about 5 mM to about 20 mM and wherein the pH is in a range of about 3.0 to about 8.0;

wherein said bulking agent is at a concentration of about 2.5% to about 4% w/v;

wherein said stabilizing agent is at a concentration of about 0.1% to about 5% w/v;

wherein said surfactant is at a concentration of about 0.004% to about 0.04% w/v; and

b) lyophilizing said therapeutic peptibody;

wherein said therapeutic peptibody comprises a structure set out in Formula I,

Formula I: $[(X^1)_a\text{-}F^1\text{-}(X^2)_b]\text{-}(L^1)_c\text{-}WSP_d$

wherein:

F^1 is an Fc domain;

X^1 is selected from

$P^1\text{-}(L^2)_e\text{-}$

$P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$

$P^3\text{-}(L^4)_g\text{-}P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$ and

$P^4\text{-}(L^5)_h\text{-}P^3\text{-}(L^4)_g\text{-}P^2\text{-}(L^3)_f\text{-}P^1\text{-}(L^2)_e\text{-}$

X^2 is selected from:

$\text{-}(L^2)_e\text{-}P^1$,

$\text{-}(L^2)_e\text{-}P^1\text{-}(L^3)_f\text{-}P^2$,

$\text{-}(L^2)_e\text{-}P^1\text{-}(L^3)_f\text{-}P^2\text{-}(L^4)_g\text{-}P^3$, and

$\text{-}(L^2)_e\text{-}P^1\text{-}(L^3)_f\text{-}P^2\text{-}(L^4)_g\text{-}P^3\text{-}(L^5)_h\text{-}P^4$

wherein P^1, P^2, P^3, and P^4 are each independently sequences of pharmacologically active peptides;

L^1, L^2, L^3, L^4, and L^5 are each independently linkers;

a, b, c, e, f, g, and h are each independently 0 or 1,

provided that at least one of a and b is 1;

d is 0, 1, or greater than 1; and

WSP is a water soluble polymer, the attachment of which is effected at any reactive moiety in F^1.

41. The method of claim 40 wherein said therapeutic peptibody comprises a structure set out in Formula II

Formula II: $[X^1\text{-}F^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the C-terminus of X^1, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

42. The method of claim 40 wherein said therapeutic peptibody comprises a structure set out in Formula III

Formula III: $[F^1\text{-}X^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of X^2, and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

43. The method of claim 40 wherein said therapeutic peptibody comprises a structure set out in Formula IV

Formula IV: $[F^1\text{-}(L^1)_e\text{-}P^1]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $-(L^1)_c\text{-}P^1$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

44. The method of claim 40 wherein said therapeutic peptibody comprises a structure set out in Formula V

Formula V: $[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}P^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein the Fc domain is attached at the N-terminus of $-L^1\text{-}P^1\text{-}L^2\text{-}P^2$ and zero, one or more WSP is attached to the Fc domain, optionally through linker L^1.

45. The method of any one of claims 40 through 44 wherein said therapeutic peptibody is a multimer.

46. The method of claim 45 wherein said therapeutic peptibody is a dimer.

47. The method of any one of claims 40 through 46 wherein P^1, P^2, P^3 and/or P^4 are independently selected from a peptide set out in any one of Tables 4 through 38.

48. The method of claim 8 wherein P^1, P^2, P^3 and/or P^4 have the same amino acid sequence.

49. The method of any one of claims 40 through 46 wherein the Fc domain is set out in SEQ ID NO:1.

50. The method of any one of claims 40 through 46 wherein WSP is PEG.

51. The method of any one of claims 40 through 46 wherein the Fc domain is set out in SEQ ID NO:1 and WSP is PEG.

52. The method of claim 51 wherein PEG has a molecular weight of between about 2 kDa and 100 kDa.

53. The method of claim 52 wherein said PEG has a molecular weight of between about 6 kDa and 25 kDa.

54. The method of claim 53, wherein said composition comprises at least 50% PEGylated therapeutic peptibody.

55. The method of claim 54 comprising at least 75% PEGylated therapeutic peptibody.

56. The method of claim 54 comprising at least 85% PEGylated therapeutic peptibody.

57. The method of claim 54 comprising at least 90% PEGylated therapeutic peptibody.

58. The method of claim 54 comprising at least 95% PEGylated therapeutic peptibody.

59. The method of any one of claims 40-58 wherein said pH buffering agent is selected from the group consisting of glycine, histidine, glutamate, succinate, phosphate, acetate, and aspartate.

60. The method of any one of claims 40-58 wherein said bulking agent selected from the group consisting of mannitol, glycine, sucrose, dextran, polyvinylpyrolidone, carboxymethylcellulose, lactose, sorbitol, trehalose, or xylitol.

61. The method of any one of claims 40-58 wherein said stabilizing agent selected from the group consisting of sucrose, trehalose, mannose, maltose, lactose, glucose, raffinose, cellobiose, gentiobiose, isomaltose, arabinose, glucosamine, fructose, mannitol, sorbitol, glycine, arginine HCL, poly-hydroxy compounds, including polysaccharides such as dextran,

starch, hydroxyethyl starch, cyclodextrins, N-methyl pyrollidene, cellulose and hyaluronic acid, sodium chloride.

62. The method of any one of claims 40-58 wherein said surfactant selected from the group consisting of sodium lauryl sulfate, dioctyl sodium sulfosuccinate, dioctyl sodium sulfonate, chenodeoxycholic acid, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, glycodeoxycholic acid sodium salt, benzalkonium chloride or benzethonium chloride, cetylpyridinium chloride monohydrate, hexadecyltrimethylammonium bromide, CHAPS, CHAPSO, SB3-10, SB3-12, digitonin, Triton X-100, Triton X-114, , lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 40, 50 and 60, glycerol monostearate, polysorbate 20, 40, 60, 65 and 80, soy lecithin, DOPC, DMPG, DMPC, and DOPG; sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose.

63. The method of any one of claims 40-58 wherein the therapeutic peptibody concentration is between about 0.25 mg/mL and 250 mg/mL.

64. The method of any one of claims 40-58 wherein said pH buffering agent is 10 mM histidine and wherein the pH is 5.0;

wherein said bulking agent is 4% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.004% w/v polysorbate-20.

65. The method of claim 64 wherein P^1 comprises a sequence set forth in Table 6.

66. The method of claim 65 wherein the therapeutic peptibody concentration is 0.5 mg/mL.

67. The method of any one of claims 40-58 wherein said pH buffering agent is 10 mM histidine and wherein the pH is 7.0;

wherein said bulking agent is 4% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.01% w/v polysorbate-20.

68. The method of claim 67 wherein P^1 comprises a sequence set forth in Table 32.

69. The method of claim 68 wherein the therapeutic peptibody concentration is 30 mg/mL.

70. The method of any one of claims 40-58 wherein said pH buffering agent is 20 mM histidine and wherein the pH is 5.0;

wherein said bulking agent is 3.3% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.01% w/v polysorbate-20.

71. The composition of claim 70 wherein P^1 comprises a sequence set forth in Table 4.

72. The method of claim 71 wherein the therapeutic peptibody concentration is 100 mg/mL.

73. The method of any one of claims 40-58 wherein said pH buffering agent is 10 mM histidine and wherein the pH is 5.0;

wherein said bulking agent is 2.5% w/v mannitol; and

wherein said stabilizing agent is 3.5% w/v sucrose.

74. The method of claim 73 wherein P^1 comprises a sequence set forth in Table 31.

75. The method of claim 74 wherein the therapeutic peptibody concentration is 30 mg/mL.

76. The method of any of claims 40-58 wherein the composition is selected from the group consisting of:

a) 10 mM histidine, pH 4.7, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20;

b) 10 mM histidine, pH 5, 4% mannitol and 2% sucrose, with and without 0.004% polysorbate-20;

c) 10 mM glutamate, pH 4.5, 4% mannitol and 2% sucrose with and without 0.004% polysorbate-20;

d) 10 mM succinate, pH 4.5, 4% mannitol and 2% sucrose, 0.004% polysorbate-20;

e) 10 mM glutamate, pH 4.5, 9% sucrose, 0.004% polysorbate-20;

f) 10 mM glutamate, pH 4.5, 4% mannitol, 2% sucrose, 1% hydroxyethyl starch, 0.004% polysorbate-20;

g) 5 mM glutamate, pH 4.5, 2% mannitol, 1% sucrose, 0.004% polysorbate-20; and

h) 10 mM glutamate, pH 4.5, 4% mannitol, 2% trehalose, 0.004% polysorbate-20.

77. The method according to claim 76 wherein P^1 comprises a sequence set forth in Tables 21-24.

78. The composition of claim 77 wherein the therapeutic peptibody concentration is selected from the group consisting of 1, 30, 85, and 100 mg/mL.

79. The method of any one of claims 40 - 75 further comprising, prior to lyophilization, the steps of:

b) adjusting the pH of the solution to a pH between about 4.0 and about 8.0;

c) preparing a solution containing said therapeutic peptibody;

d) buffer exchanging the solution of step (c) into the solution of step (b);

e) adding an appropriate amount of a surfactant; and

f) lyophilizing the mixture from step (e).

80. A method for preparing a reconstituted therapeutic peptibody composition comprising the steps of:

a) lyophilizing a therapeutic peptibody composition according to any one of claims 40- 78; and

b) reconstituting said lyophilized therapeutic peptibody composition.

81. A kit for preparing an aqueous pharmaceutical composition comprising a first container having a lyophilized therapeutic peptibody composition of any one of claims 1 through 36, and a second container having a physiologically acceptable solvent for the lyophilized composition.

SEQUENCE LISTING

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<160> 1701

<170> PatentIn version 3.3

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

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

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

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

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

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

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

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

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

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

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
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Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
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            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
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210 215 220

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225 230 235 240

Trp Asp Pro Trp Thr Cys Glu His Met Gly Ser Gly Ser Ala Thr Gly
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Gly Leu

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<400> 17

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

<210> 18
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<212> PRT
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<400> 18

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1 5 10

<210> 19
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<212> PRT
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<220>
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<223> Acetylated phenylalanine at position 1

<220>
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<223> Azetidine is between positions 9 and 10

<400> 19

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1 5 10

<210> 20
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<212> PRT
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<223> Phosphorylated Tyr at position 8

<220>
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<222> (10)..(11)
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<400> 20

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

<210> 21
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<400> 21

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1 5 10

<210> 22
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<220>
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<223> Azetidine is between residues 9 and 10

<400> 22

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1 5 10

<210> 23
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1 5 10

<210> 24
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<223> Acetylated phenylalanine at position 1

<220>
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<223> Azetidine is between residues 9 and 10

<400> 25

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1 5 10

<210> 26
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1 5 10

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<223> Xaa=Sarcosine

<220>
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<223> Azetidine is between residues 9 and 10

<400> 27

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1 5 10

<210> 28
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<220>
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<400> 28

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

<210> 29
<211> 11
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<220>
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<400> 29

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

<210> 30
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<220>
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<400> 30

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1 5 10

<210> 31
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<400> 31

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<220>
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<222> (8)..(9)
<223> Azetidine is between residues 8 and 9

<400> 32

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<210> 33
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<223> Aminoisobutyric acid is between residues 5 and 6

<220>
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<222> (8)..(9)
<223> Azetidine is between residues 8 and 9

<400> 33

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<210> 34
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<400> 34

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<210> 35
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<212> PRT
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<400> 35

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

<210> 36
<211> 11
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<220>
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<400> 36

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

<210> 37
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<220>
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<400> 37

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1 5 10

<210> 38
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<220>
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<223> Azetidine is between residues 9 and 10

<400> 38

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1 5 10

<210> 39
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<220>
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<223> Phosphorylated Tyr at position 8

<220>
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<222> (9)..(10)
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<400> 39

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1 5 10

<210> 40
<211> 10
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<220>
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<400> 40

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1 5 10

<210> 41
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<400> 41

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1 5 10

<210> 42
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<220>
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<400> 42

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

<210> 43
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<220>
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<400> 43

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

<210> 44
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<223> Acetylated phenylalanine at position 1

<220>
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<400> 44

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<210> 45
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<223> D-Ala

<220>
<221> Misc_feature
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<223> Azetidine is between residues 9 and 10

<400> 45

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1 5 10

<210> 46
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<223> Xaa=Sarcosine

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<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 46

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1 5 10

<210> 47
<211> 11
<212> PRT
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<400> 47

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

<210> 48
<211> 11
<212> PRT
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<400> 48

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

<210> 49
<211> 11
<212> PRT
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<400> 49

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

<210> 50
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<223> D-Val

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1 5 10

<210> 51
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<223> Pipecolic acid is between residues 4 and 5

<220>
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<222> (8)..(9)
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<400> 51

Phe Glu Trp Thr Gly Tyr Trp Gln Tyr

1 5

<210> 52
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<223> Aminoisobutyric acid is between residues 5 and 6

<220>
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<222> (8)..(9)
<223> Azetidine is between residues 8 and 9

<400> 52

Phe Glu Trp Thr Pro Tyr Trp Gln Tyr
1 5

<210> 53
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<222> (5)..(5)
<223> Xaa=Sarcosine

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<222> (9)..(10)
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<400> 53

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

<210> 54
<211> 15
<212> PRT
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<220>
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<400> 54

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

<210> 55
<211> 10

<212> PRT
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<223> Ala modified to 1-naphthylalanine at position 1

<220>
<222> (9)..(10)
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<400> 55

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

<210> 56
<211> 10
<212> PRT
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<220>
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<220>
<221> Misc_feature
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<400> 56

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

<210> 57
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<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 57

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

<210> 58
<211> 10
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<220>
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<400> 58

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

<210> 59
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<220>
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<400> 59

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

<210> 60
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<400> 60

Thr Lys Pro Arg
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<210> 61
<211> 5
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<400> 61

Arg Lys Ser Ser Lys
1 5

<210> 62
<211> 5
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<220>
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<400> 62

Arg Lys Gln Asp Lys
1 5

<210> 63
<211> 6
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<220>
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<400> 63

Asn Arg Lys Gln Asp Lys
1 5

<210> 64
<211> 6
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<400> 64

Arg Lys Gln Asp Lys Arg
1 5

<210> 65
<211> 9
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<220>
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<400> 65

Glu Asn Arg Lys Gln Asp Lys Arg Phe
1 5

<210> 66
<211> 6
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<220>
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<400> 66

Val Thr Lys Phe Tyr Phe
1 5

<210> 67
<211> 5
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<220>
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<400> 67

Val Thr Lys Phe Tyr
1 5

<210> 68
<211> 5
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<400> 68

Val Thr Asp Phe Tyr
1 5

<210> 69
<211> 11
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<220>
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<400> 69

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

<210> 70
<211> 12
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<220>
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<400> 70

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

<210> 71
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<220>

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<400> 71

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

<210> 72
<211> 12
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<400> 72

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

<210> 73
<211> 12
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<400> 73

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

<210> 74
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<400> 74

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

<210> 75
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<400> 75

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

<210> 76
<211> 12
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<400> 76

Ser Val Val Phe Trp Gln Pro Tyr Ser Val Gln Thr
1 5 10

<210> 77
<211> 12
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<400> 77

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

<210> 78
<211> 12
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<220>
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<400> 78

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

<210> 79
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<400> 79

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

<210> 80
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<400> 80

Ser Pro Val Phe Trp Gln Pro Tyr Ser Ile Gln Ile
1 5 10

<210> 81
<211> 12

<212> PRT
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<220>
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<400> 81

Trp Ile Glu Trp Trp Gln Pro Tyr Ser Val Gln Ser
1 5 10

<210> 82
<211> 12
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<400> 82

Ser Leu Ile Tyr Trp Gln Pro Tyr Ser Leu Gln Met
1 5 10

<210> 83
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<400> 83

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

<210> 84
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<400> 84

Arg Cys Asp Tyr Trp Gln Pro Tyr Ser Val Gln Thr
1 5 10

<210> 85
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Met Arg Val Phe Trp Gln Pro Tyr Ser Val Gln Asn
1 5 10

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<400> 86

Lys Ile Val Tyr Trp Gln Pro Tyr Ser Val Gln Thr
1 5 10

<210> 87
<211> 12
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<400> 87

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

<210> 88
<211> 12
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<220>
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<400> 88

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

<210> 89
<211> 12
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<220>
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<400> 89

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

<210> 90
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<400> 90

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

<210> 91
<211> 12
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<400> 91

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

<210> 92
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<400> 92

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

<210> 93
<211> 12
<212> PRT
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<220>
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<400> 93

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

<210> 94
<211> 12
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<220>
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<400> 94

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

<210> 95
<211> 12
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<220>
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<400> 95

Asn Gly Asn Tyr Trp Gln Pro Tyr Ser Phe Gln Val
1 5 10

<210> 96
<211> 12
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<400> 96

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

<210> 97
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<400> 97

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

<210> 98
<211> 12
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<400> 98

Asn Leu Leu Tyr Trp Gln Pro Tyr Ser Met Gln Asp
1 5 10

<210> 99
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<400> 99

Gly Tyr Glu Trp Tyr Gln Pro Tyr Ser Val Gln Arg
1 5 10

<210> 100
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<400> 100

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

<210> 101
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<400> 101

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

<210> 102
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<400> 102

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

<210> 103
<211> 12
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<400> 103

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

<210> 104
<211> 12
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<400> 104

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

<210> 105
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<400> 105

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

<210> 106
<211> 12
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<400> 106

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

<210> 107
<211> 12
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<400> 107

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

<210> 108
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<400> 108

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

<210> 109
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Gly Arg Val Trp Phe Gln Pro Tyr Ser Val Gln Arg
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Ala Arg Thr Trp Tyr Gln Pro Tyr Ser Val Gln Arg
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Ala Arg Val Trp Trp Gln Pro Tyr Ser Val Gln Met
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Arg Leu Met Phe Tyr Gln Pro Tyr Ser Val Gln Arg
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Glu Ser Met Trp Tyr Gln Pro Tyr Ser Val Gln Arg
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His Phe Gly Trp Trp Gln Pro Tyr Ser Val His Met
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Ala Arg Phe Trp Trp Gln Pro Tyr Ser Val Gln Arg
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Arg Leu Val Tyr Trp Gln Pro Tyr Ala Pro Ile Tyr
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Arg Leu Val Tyr Trp Gln Pro Tyr Ser Tyr Gln Thr
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Arg Leu Val Tyr Trp Gln Pro Tyr Ser Leu Pro Ile
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Ser Arg Val Trp Tyr Gln Pro Tyr Ala Lys Gly Leu
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Ser Arg Val Trp Tyr Gln Pro Tyr Ala Gln Gly Leu
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Ser Arg Val Trp Tyr Gln Pro Tyr Ser Leu Gly Leu
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Ser Arg Val Trp Tyr Gln Pro Tyr Ala Arg Glu Leu
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Glu Tyr Glu Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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Asp Pro Leu Phe Trp Gln Pro Tyr Ala Leu Pro Leu
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Trp Ser Gly Tyr Phe Gln Pro Tyr Ala Leu Pro Leu
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Tyr Tyr Gln Pro Tyr Ala Leu Pro Leu
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Tyr Phe Gln Pro Tyr Ala Leu Gly Leu
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Tyr Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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Arg Trp Trp Gln Pro Tyr Ala Thr Pro Leu
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Gly Trp Tyr Gln Pro Tyr Ala Leu Gly Phe
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Tyr Trp Tyr Gln Pro Tyr Ala Leu Gly Leu
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Ile Trp Tyr Gln Pro Tyr Ala Met Pro Leu
1 5 10

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Ser Asn Met Gln Pro Tyr Gln Arg Leu Ser
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Thr Ala Cys Asn
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Lys Val Thr Met
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Gly Phe Pro Leu
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His Val Arg His
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Ala Val Arg Ala
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<400> 166

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Ile Ala Gln Val
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Gly Trp Tyr Gln Pro Tyr Val Asp Gly Trp Arg
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Arg Trp Glu Gln Pro Tyr Val Lys Asp Gly Trp Ser
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Glu Trp Tyr Gln Pro Tyr Ala Leu Gly Trp Ala Arg
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Leu Phe Glu Gln Pro Tyr Ala Lys Ala Leu Gly Leu
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Gly Trp Glu Gln Pro Tyr Ala Arg Gly Leu Ala Gly
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<400> 173

Ala Trp Val Gln Pro Tyr Ala Thr Pro Leu Asp Glu
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Met Trp Tyr Gln Pro Tyr Ser Ser Gln Pro Ala Glu
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Gly Trp Thr Gln Pro Tyr Ser Gln Gln Gly Glu Val

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Asp Trp Phe Gln Pro Tyr Ser Ile Gln Ser Asp Glu
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Pro Trp Ile Gln Pro Tyr Ala Arg Gly Phe Gly
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Arg Pro Leu Tyr Trp Gln Pro Tyr Ser Val Gln Val
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Arg Phe Asp Tyr Trp Gln Pro Tyr Ser Asp Gln Thr
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Trp His Gln Phe Val Gln Pro Tyr Ala Leu Pro Leu
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Ser Asp Val Val Tyr Trp Gln Pro Tyr Ser Val Gln Ser Leu Glu Met
1 5 10 15

<210> 185
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Ala

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Gln Arg Ile Trp Trp Gln Pro Tyr Ala Leu Pro Leu
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Asp Tyr Val Trp Gln Gln Pro Tyr Ala Leu Pro Leu
1 5 10

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Met Asp Leu Leu Val Gln Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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Arg Gln Gly Ala Asn Ile Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<400> 202

Lys Lys Gly Ser Thr Gln Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<400> 203

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<210> 204

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Glu Pro Arg Ser Gln Lys Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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Val Lys Gln Lys Trp Arg Trp Tyr Gln Pro Tyr Ala Leu Pro Leu
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<210> 206
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Glu Arg Met Trp Gln Pro Tyr Ala Leu Pro Leu
1 5 10

<210> 223
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<222> (2)..(3)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (5)..(6)
<223> Xaa can be any naturally occurring amino acid

<400> 223

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

<210> 224
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 224

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

<210> 225
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 225

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

<210> 226
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 226

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

<210> 227
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<400> 227

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

<210> 228
<211> 12
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<220>
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<220>
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<222> (5)..(6)
<223> Xaa can be any naturally occurring amino acid

<400> 228

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

<210> 229
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 229

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

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<400> 230

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

<210> 231
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<220>
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<400> 231

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

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<400> 232

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

<210> 233
<211> 12
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<220>
<223> Synthetic peptide

<400> 233

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

<210> 234
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<400> 234

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

<210> 235
<211> 12
<212> PRT
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<220>
<223> Synthetic peptide

<400> 235

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

<210> 236
<211> 12
<212> PRT
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<220>
<223> Synthetic peptide

<400> 236

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

<210> 237
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<213> Artificial sequence

<220>
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<400> 237

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

<210> 238
<211> 12
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<213> Artificial sequence

<220>
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<400> 238

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

<210> 239
<211> 12
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<220>
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<400> 239

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

<210> 240
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<220>

<223> Synthetic peptide

<400> 240

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

<210> 241
<211> 17
<212> PRT
<213> Artificial sequence

<220>
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<400> 241

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

Gly

<210> 242
<211> 17
<212> PRT
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<220>
<223> Synthetic peptide

<400> 242

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

Glu

<210> 243
<211> 17
<212> PRT
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<220>
<223> Synthetic peptide

<400> 243

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

Ala

<210> 244
<211> 17
<212> PRT
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<220>

<223> Synthetic peptide

<400> 244

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

Asp

<210> 245
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 245

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

Pro

<210> 246
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 246

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

Ser

<210> 247
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 247

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

<210> 248
<211> 10
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 248

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

<210> 249
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 249

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

<210> 250
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 250

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

<210> 251
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 251

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

<210> 252
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 252

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

<210> 253
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 253

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

<210> 254
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 254

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

Tyr Ala Leu Pro Leu
20

<210> 255
<211> 21
<212> PRT
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<220>
<223> Synthetic peptide

<400> 255

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

Tyr Ala Leu Pro Leu
20

<210> 256
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 256

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

Tyr Ala Leu Pro Leu
20

<210> 257
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 257

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

Tyr Ala Leu Pro Leu
20

<210> 258
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 258

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

Tyr Ala Leu Pro Leu
20

<210> 259
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 259

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

Tyr Ala Leu Pro Leu
20

<210> 260
<211> 21
<212> PRT
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<220>
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<400> 260

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

Tyr Ala Leu Pro Leu
20

<210> 261
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 261

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

Tyr Ala Leu Pro Leu
20

<210> 262
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 262

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

Tyr Ala Leu Pro Leu
20

<210> 263
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 263

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

Tyr Ala Leu Pro Leu
20

<210> 264
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 264

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

Tyr Ala Leu Pro Leu
20

<210> 265
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 265

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

<210> 266
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 266

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

Tyr Ala Leu Pro Leu
20

<210> 267
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 267

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

Ala Leu Pro Leu
20

<210> 268
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 268

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

Tyr Ala Leu Pro Leu
20

<210> 269
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 269

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

Tyr Ala Leu Pro Leu
20

<210> 270
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 270

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

Tyr Ala Leu Pro Leu
20

<210> 271
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 271

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

Tyr Ala Leu Pro Leu
20

<210> 272
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 272

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

Tyr Ala Leu Pro Leu
20

<210> 273
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 273

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

Tyr Ala Leu Pro Leu
20

<210> 274
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 274

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

Tyr Ala Leu Pro Leu
20

<210> 275
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 275

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

Tyr Ala Leu Pro Leu
20

<210> 276
<211> 21
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 276

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

Tyr Ala Leu Pro Leu
20

<210> 277
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 277

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

Tyr Ala Leu Pro Leu
20

<210> 278
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 278

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

Tyr Ala Leu Pro Leu
20

<210> 279
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 279

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

Tyr Ala Leu Pro Leu
20

<210> 280
<211> 21

<212> PRT
<213> Artificial sequence

<220>
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<400> 280

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

Tyr Ala Leu Pro Leu
20

<210> 281
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 281

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

Tyr Ala Leu Pro Leu
20

<210> 282
<211> 21
<212> PRT
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<220>
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<400> 282

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

Tyr Ala Leu Pro Leu
20

<210> 283
<211> 21
<212> PRT
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<220>
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<400> 283

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

Tyr Ala Leu Pro Leu
20

<210> 284
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 284

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

Tyr Ala Leu Pro Leu
20

<210> 285
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 285

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

Ala Leu Pro Leu
20

<210> 286
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 286

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

Tyr Ala Leu Pro Leu
20

<210> 287
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 287

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

Tyr Ala Leu Pro Leu
20

<210> 288
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<220>
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<400> 288

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

Tyr Ala Leu Pro Leu
20

<210> 289
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 289

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

Tyr Ala Leu Pro Leu
20

<210> 290
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 290

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

Tyr Ala Leu Pro Leu
20

<210> 291
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 291

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

Tyr Ala Leu Pro Leu
20

<210> 292
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 292

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

Tyr Ala Leu Pro Leu
20

<210> 293
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 293

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

Tyr Ala Leu Pro Leu
20

<210> 294
<211> 7
<212> PRT
<213> Artificial sequence

<220>
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<400> 294

Gln Pro Tyr Ala Leu Pro Leu
1 5

<210> 295
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<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Xaa=Unsure

<220>
<221> Misc_feature
<222> (2)..(2)
<223> Ala modified to 1-naphthylalanine at position 2

<220>
<221> Misc_feature
<222> (5)..(6)
<223> Azetidine is between residues 5 and 6

<400> 295

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

<210> 296
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 296

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

Tyr Ala Leu Pro Leu
20

<210> 297
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 297

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

<210> 298
<211> 14
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<220>
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<220>
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<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 298

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

<210> 299
<211> 14
<212> PRT
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 299

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

<210> 300
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 300

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

Tyr Ala Leu Pro Leu
20

<210> 301
<211> 17
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (12)..(13)
<223> Azetidine is between residues 12 and 13

<400> 301

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

Leu

<210> 302
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 302

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

<210> 303
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 303

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

Leu

<210> 304
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 304

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

Gly Leu

<210> 305
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 305

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

<210> 306
<211> 14
<212> PRT

<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 306

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

<210> 307
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 307

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

<210> 308
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 308

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

<210> 309
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 309

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

<210> 310
<211> 14
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<213> Artificial sequence

<220>
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<220>
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<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 310

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

<210> 311
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 311

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

Tyr Ala Leu Pro Leu
20

<210> 312
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 312

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

Gly Leu

<210> 313
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 313

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

Tyr Ala Leu Pro Leu

20

<210> 314
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 314

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

Tyr Ala Leu Pro Leu
20

<210> 315
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 315

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

Tyr Ala Leu Pro Leu
20

<210> 316
<211> 21
<212> PRT
<213> Artificial sequence

<220>
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<400> 316

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

Tyr Ala Leu Pro Leu
20

<210> 317
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 317

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

<210> 318
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 318

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

<210> 319
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 319

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

<210> 320
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 320

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

<210> 321
<211> 10
<212> PRT
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 321

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

<210> 322
<211> 10
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 322

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

<210> 323
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 323

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

<210> 324
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 324

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

<210> 325
<211> 10
<212> PRT
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 325

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

<210> 326
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
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<223> Azetidine is between residues 9 and 10

<400> 326

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

<210> 327
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 327

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

<210> 328
<211> 10
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<220>
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<220>
<221> Misc_feature

<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 328

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

<210> 329
<211> 10
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 329

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

<210> 330
<211> 10
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<220>
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<220>
<221> Misc_feature
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<223> Azetidine is between residues 9 and 10

<400> 330

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

<210> 331
<211> 10
<212> PRT
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<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 331

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

<210> 332
<211> 10
<212> PRT
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<220>
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<220>
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<222> (5)..(5)
<223> D-Pro

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 332

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

<210> 333
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (4)..(5)
<223> Azetidine is between residues 4 and 5

<220>
<221> Misc_feature
<222> (8)..(9)
<223> Azetidine is between residues 8 and 9

<400> 333

Phe Glu Trp Thr Gly Tyr Trp Gln Tyr
1 5

<210> 334
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
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<223> Pipecolic acid is between residues 4 and 5

<220>
<221> Misc_feature
<222> (8)..(9)
<223> Azetidine is between residues 8 and 9

<400> 334

Phe Glu Trp Thr Gly Tyr Trp Gln Tyr
1 5

<210> 335
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (5)..(6)
<223> Aminoisobutyric acid is between residues 5 and 6

<220>
<221> Misc_feature
<222> (8)..(9)
<223> Azetidine is between residues 8 and 9

<400> 335

Phe Glu Trp Thr Pro Tyr Trp Gln Tyr
1 5

<210> 336
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=Sarcosine

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 336

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

<210> 337
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>

<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Sarcosine

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 337

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

<210> 338
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 338

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

<210> 339
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 339

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

<210> 340
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 340

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

<210> 341
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Acetylation
<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 341

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

<210> 342
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Acetylation
<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 342

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

<210> 343
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature

<222> (1)..(1)
<223> Ala modified to 1-naphthylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 343

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

<210> 344
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 344

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

<210> 345
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 345

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

<210> 346
<211> 10
<212> PRT
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<220>
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<220>
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<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 346

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

<210> 347
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 347

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

<210> 348
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 348

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

<210> 349
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Ala modified to 1-naphthylalanine at position 5

<400> 349

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

<210> 350
<211> 12

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Ala modified to 1-naphthylalanine at position 5

<400> 350

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

<210> 351
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (5)..(5)
<223> Ala modified to 1-naphthylalanine at position 5

<400> 351

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

<210> 352
<211> 12
<212> PRT
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<220>
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<220>
<221> Misc_feature
<222> (5)..(5)
<223> Ala modified to 1-naphthylalanine at position 5

<400> 352

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

<210> 353
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 353

Val Tyr Trp Gln Pro Tyr Ser Val Gln
1 5

<210> 354
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Ala modified to 1-naphthylalanine at position 5

<400> 354

Val Tyr Ala Gln Pro Tyr Ser Val Gln
1 5

<210> 355
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (6)..(7)
<223> Azetidine is between residues 6 and 7

<400> 355

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

<210> 356
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<220>
<221> Misc_feature
<222> (10)..(10)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 10

<400> 356

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

<210> 357
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<220>
<221> Misc_feature
<222> (10)..(10)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 10

<400> 357

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

<210> 358
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (8)..(8)
<223> Xaa=p-benzoyl-L-phenylalanine

<220>
<221> Misc_feature
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<223> Azetidine is between residues 9 and 10

<400> 358

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

<210> 359
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature

<222> (8)..(8)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 8

<220>
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<222> (9)..(10)
<223> Azetidine is between positions 9 and 10

<400> 359

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

<210> 360
<211> 10
<212> PRT
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<220>
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<220>
<221> Misc_feature
<222> (7)..(7)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 7

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 360

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

<210> 361
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
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<222> (7)..(7)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 7

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 361

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

<210> 362
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Acetylation
<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 3

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 362

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

<210> 363
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 3

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 363

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

<210> 364
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (1)..(1)
<223> Phe modified to p-benzoyl-L-phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 364

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

<210> 365
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Phe modified to acetylated p-benzoyl-L-phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 365

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

<210> 366
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 366

Val Tyr Trp Gln Pro Tyr Ser Val Gln
1 5

<210> 367
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 367

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

<210> 368
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Ala modified to 1-naphthylalanine at position 5

<400> 368

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

<210> 369
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 369

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

<210> 370
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 370

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

<210> 371
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 371

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

<210> 372
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 372

Asp Asn Ser Ser Trp Tyr Asp Ser Phe Leu Leu
1 5 10

<210> 373
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 373

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

<210> 374
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<400> 374

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

<210> 375
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 375

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

Cys

<210> 376
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 376

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

Gln

<210> 377
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 377

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

Gly

<210> 378
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 378

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

Tyr

<210> 379
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 379

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

Tyr

<210> 380
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 380

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

Tyr

<210> 381
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 381

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

Tyr

<210> 382
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 382

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

Tyr

<210> 383
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 383

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

Gln

<210> 384
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 384

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

Asp

<210> 385
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 385

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

Pro

<210> 386
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 386

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

Ala

<210> 387
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 387

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

Ala

<210> 388
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 388

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

Thr

<210> 389
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 389

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

Leu

<210> 390
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 390

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

His

<210> 391
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 391

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

Tyr Ala Leu Pro Leu
20

<210> 392
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 392

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

Tyr Ala Leu Pro Leu
20

<210> 393
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 393

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

Tyr Ala Leu Pro Leu
20

<210> 394
<211> 9
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<220>
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<220>
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<222> (1)..(1)
<223> Phosphotyrosine at position 1

<220>
<221> Misc_feature
<222> (2)..(2)
<223> Ala modified to 1-naphthylalanine at position 2

<220>
<221> Phosphorylation
<222> (3)..(3)
<223> Phosphotyrosine at position 3

<220>
<221> Misc_feature
<222> (4)..(5)
<223> Azetidine is between residues 4 and 5

<400> 394

Tyr Ala Tyr Gln Tyr Ala Leu Pro Leu
1 5

<210> 395
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 395

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

Tyr Ala Leu Pro Leu
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<210> 396
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 396

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

<210> 397
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 397

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

Asp

<210> 398
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 398

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

<210> 399
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 399

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

<210> 400
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 400

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

<210> 401
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 401

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

<210> 402
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 402

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

<210> 403
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Acetylation
<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 403

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

<210> 404
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 404

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

<210> 405
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 405

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

<210> 406
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 406

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

<210> 407
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 407

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

<210> 408
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 408

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

<210> 409
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 409

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

Tyr Ala Leu Pro Leu
20

<210> 410
<211> 10
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<220>
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<220>
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<223> Acetylated phenylalanine at position 1

<220>
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<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 410

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

<210> 411
<211> 10
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<220>
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<220>
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<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 411

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

<210> 412
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 412

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

<210> 413
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
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<222> (1)..(1)
<223> Acetylated phenylalanine at position 1

<220>
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<222> (6)..(6)
<223> D-Ala

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 413

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

<210> 414
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<220>
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<222> (6)..(6)
<223> D-Ala

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 414

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

<210> 415
<211> 10
<212> PRT
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<220>
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<220>
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<223> Acetylated phenylalanine at position 1

<220>
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<222> (6)..(6)
<223> D-Ala

<220>
<221> Misc_feature
<222> (9)..(10)
<223> Azetidine is between residues 9 and 10

<400> 415

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

<210> 416
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<212> PRT
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<220>
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<220>
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<220>
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<222> (4)..(5)
<223> Xaa can be any naturally occurring amino acid

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<222> (8)..(8)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (11)..(11)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (13)..(13)
<223> Xaa can be any naturally occurring amino acid

<400> 416

Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro
1 5 10

<210> 417
<211> 14
<212> PRT
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<222> (4)..(5)
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<222> (8)..(8)
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<220>
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<222> (13)..(13)
<223> Xaa can be any naturally occurring amino acid

<400> 417

Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro
1 5 10

<210> 418
<211> 14
<212> PRT
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<220>
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<220>
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<222> (4)..(5)
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<222> (8)..(8)
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<220>
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<222> (13)..(13)
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<400> 418

Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro
1 5 10

<210> 419
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<220>
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<222> (4)..(5)
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<222> (8)..(8)
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<222> (11)..(11)
<223> Xaa can be any naturally occurring amino acid

<220>
<221> Misc_feature
<222> (13)..(13)
<223> Xaa can be any naturally occurring amino acid

<400> 419

Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Pro
1 5 10

<210> 420
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 420

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly
20

<210> 421
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 421

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

Pro Leu Gly Gly
20

<210> 422
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 422

Gly Gly Val Tyr Ala Cys Arg Met Gly Pro Ile Thr Trp Val Cys Ser
1 5 10 15

Pro Leu Gly Gly
20

<210> 423
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 423

Val Gly Asn Tyr Met Cys His Phe Gly Pro Ile Thr Trp Val Cys Arg
1 5 10 15

Pro Gly Gly Gly
20

<210> 424
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 424

Gly Gly Leu Tyr Leu Cys Arg Phe Gly Pro Val Thr Trp Asp Cys Gly
1 5 10 15

Tyr Lys Gly Gly
20

<210> 425
<211> 40
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 425

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr
20 25 30

Trp Val Cys Lys Pro Gln Gly Gly
35 40

<210> 426
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 426

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly
20

<210> 427
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 427

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys
20

<210> 428
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 428

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys
20

<210> 429
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 429

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys
20

<210> 430
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 430

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser
20

<210> 431
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 431

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly Ser Ser Lys
20

<210> 432
<211> 10
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<220>
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<223> Xaa=Arg, His, Leu or Trp

<220>
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<222> (3)..(3)
<223> Xaa=Met, Phe or Ile

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=any amino acid

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<222> (7)..(7)
<223> Xaa=Asp, Glu, Ile, Leu or Val

<220>
<221> Misc_feature
<222> (9)..(9)
<223> Xaa=any amino acid

<400> 432

Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys
1 5 10

<210> 433
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 433

Gly Gly Thr Tyr Ser Cys His Gly Pro Leu Thr Trp Val Cys Lys Pro
1 5 10 15

Gln Gly Gly

<210> 434
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 434

Val Gly Asn Tyr Met Ala His Met Gly Pro Ile Thr Trp Val Cys Arg
1 5 10 15

Pro Gly Gly

<210> 435
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 435

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

Ile Cys

<210> 436
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 436

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln

<210> 437
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 437

Gly Gly Leu Tyr Ala Cys His Met Gly Pro Met Thr Trp Val Cys Gln
1 5 10 15

Pro Leu Arg Gly
20

<210> 438
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 438

Thr Ile Ala Gln Tyr Ile Cys Tyr Met Gly Pro Glu Thr Trp Glu Cys
1 5 10 15

Arg Pro Ser Pro Lys Ala
20

<210> 439
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 439

Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10

<210> 440
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 440

Tyr Cys His Phe Gly Pro Leu Thr Trp Val Cys
1 5 10

<210> 441
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (1)..(1)
<223> Xaa=Cys, Ala, or nothing

<220>
<221> Misc_feature
<222> (1)..(2)
<223> If residue 1 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid or homocysteine (HOC) is before residue 2

<220>
<221> Misc_feature
<222> (2)..(2)
<223> Xaa=Arg, His, Leu, or Trp

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Xaa=Met, Phe, or Ile

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (9)..(9)
<223> Xaa=Asp, Glu, Ile, Leu, or Val

<220>
<221> Misc_feature
<222> (9)..(9)
<223> If residue 10 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid
or homocysteine (HOC) is after residue 9

<220>
<221> Misc_feature
<222> (10)..(10)
<223> Xaa=Cys, Ala, or nothing

<400> 441

Xaa Xaa Xaa Gly Pro Xaa Thr Trp Xaa Xaa
1 5 10

<210> 442
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (2)..(2)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (2)..(3)
<223> If residue 3 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid
or homocysteine (HOC) is between residues 2 and 3

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Xaa=Cys, Ala, or nothing

<220>
<221> Misc_feature
<222> (4)..(4)
<223> Xaa=Arg, His, Leu, or Trp

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Met, Phe, or Ile

<220>
<221> Misc_feature
<222> (8)..(8)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Met, Phe, or Ile

<220>

<221> Misc_feature
<222> (8)..(8)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (11)..(11)
<223> Xaa=Asp, Glu, Ile, Leu, or Val

<220>
<221> Misc_feature
<222> (11)..(11)
<223> If residue 12 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid or homocysteine (HOC) is after residue 11

<220>
<221> Misc_feature
<222> (12)..(12)
<223> Xaa=Cys, Ala, or nothing

<400> 442

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

<210> 443
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (1)..(1)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (3)..(4)
<223> If residue 4 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid or homocysteine (HOC) is between residues 3 and 4

<220>
<221> Misc_feature
<222> (4)..(4)
<223> Xaa=Cys, Ala, or nothing

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Arg, His, Leu, or Trp

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=Met, Phe, or Ile

<220>
<221> Misc_feature

<222> (9)..(9)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (12)..(12)
<223> Xaa=Asp, Glu, Ile, Leu, or Val

<220>
<221> Misc_feature
<222> (12)..(13)
<223> If residue 13 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid
or homocysteine (HOC) is between residues 12 and 13

<220>
<221> Misc_feature
<222> (13)..(13)
<223> Xaa=Cys, Ala, or nothing

<220>
<221> Misc_feature
<222> (14)..(14)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (15)..(15)
<223> Xaa=any amino acid

<220>
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<222> (16)..(16)
<223> Xaa=any amino acid

<400> 443

Xaa Tyr Xaa Xaa Xaa Xaa Gly Pro Xaa Thr Trp Xaa Xaa Xaa Xaa Xaa
1 5 10 15

<210> 444
<211> 16
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (1)..(1)
<223> Xaa=any amino acid

<220>
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<222> (3)..(3)
<223> Xaa=any amino acid

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<222> (5)..(5)
<223> Xaa=Arg, His, Leu or Trp

<220>
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<223> Xaa=Met, Phe or Ile

<220>
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<222> (9)..(9)
<223> Xaa=any amino acid

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<222> (12)..(12)
<223> Xaa=Asp, Glu, Ile, Leu or Val

<220>
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<222> (14)..(14)
<223> Xaa=any amino acid

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<222> (15)..(15)
<223> Xaa=any amino acid

<220>
<221> misc_feature
<222> (16)..(16)
<223> Xaa=any amino acid

<400> 444

Xaa Tyr Xaa Cys Xaa Xaa Gly Pro Xaa Thr Trp Xaa Cys Xaa Xaa Xaa
1 5 10 15

<210> 445
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 445

Gly Gly Leu Tyr Leu Cys Arg Phe Gly Pro Val Thr Trp Asp Cys Gly
1 5 10 15

Tyr Lys Gly Gly
20

<210> 446
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 446

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln Gly Gly
20

<210> 447
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 447

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

Pro Leu Gly Gly
20

<210> 448
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 448

Val Gly Asn Tyr Met Cys His Phe Gly Pro Ile Thr Trp Val Cys Arg
1 5 10 15

Pro Gly Gly Gly
20

<210> 449
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 449

Gly Gly Val Tyr Ala Cys Arg Met Gly Pro Ile Thr Trp Val Cys Ser
1 5 10 15

Pro Leu Gly Gly
20

<210> 450
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 450

Val Gly Asn Tyr Met Ala His Met Gly Pro Ile Thr Trp Val Cys Arg
1 5 10 15

Pro Gly Gly

<210> 451
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 451

Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10 15

Pro Gln

<210> 452
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 452

Gly Gly Leu Tyr Ala Cys His Met Gly Pro Met Thr Trp Val Cys Gln
1 5 10 15

Pro Leu Arg Gly
20

<210> 453
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 453

Thr Ile Ala Gln Tyr Ile Cys Tyr Met Gly Pro Glu Thr Trp Glu Cys
1 5 10 15

Arg Pro Ser Pro Lys Ala
20

<210> 454
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 454

Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10

<210> 455
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 455

Tyr Cys His Phe Gly Pro Leu Thr Trp Val Cys
1 5 10

<210> 456
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 456

Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys
1 5 10

<210> 457
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(1)
<223> Xaa=any amino acid except Tyrosine

<220>
<221> Misc_feature
<222> (1)..(2)
<223> If residue 2 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid or homocysteine (HOC)is between residues 1 and 2

<220>
<221> Misc_feature
<222> (2)..(2)
<223> Xaa=Cys, Ala, or nothing

<220>
<221> Misc_feature
<222> (4)..(4)
<223> Xaa=Arg, His, Leu, or Trp

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Met, Phe or Ile

<220>

<221> Misc_feature
<222> (8)..(8)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (11)..(11)
<223> Xaa=Asp, Gly, Ile, Leu, or Val

<220>
<221> Misc_feature
<222> (11)..(11)
<223> If residue 12 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid
or homocysteine (HOC)is after residue 11

<220>
<221> Misc_feature
<222> (12)..(12)
<223> Xaa=Cys, Ala, or nothing

<400> 457

Xaa Xaa Xaa Xaa Xaa Gly Pro Xaa Thr Trp Xaa Xaa
1 5 10

<210> 458
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (1)..(1)
<223> Xn=Glu, Gly, Asn, Ser, Asp, Gln, Leu, Tyr, Ala, or nothing

<220>
<221> Misc_feature
<222> (2)..(2)
<223> Xn=Phe, Val, Ala, Lys, Arg, Gly, Ser, Ile, Leu, or nothing

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Xn=His, Gln, Glu, Gly, Asp, Ala, or Val

<220>
<221> Misc_feature
<222> (4)..(4)
<223> Xn=Glu, Gly, Val, Ala, Pro, Asp, Thr, or Met

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (7)..(7)
<223> Xaa=any amino acid

<220>
<221> Misc_feature
<222> (11)..(12)
<223> If residue 12 is not Cys or Ala, alpha-amino-gamma-bromobutyric acid

or homocysteine (HOC)is between residues 11 and 12

<220>
<221> Misc_feature
<222> (12)..(12)
<223> Xaa=Cys, Ala, or nothing

<220>
<221> Misc_feature
<222> (14)..(14)
<223> Xaa=Arg, His, Leu, or Trp

<220>
<221> Misc_feature
<222> (15)..(15)
<223> Xaa=Met, Phe, or Ile

<220>
<221> Misc_feature
<222> (17)..(17)
<223> Xaa=Leu, Ile, Pro, Phe, Met, Gln, or Gly

<400> 458

Xaa Xaa Xaa Xaa Cys Xaa Xaa Gly Trp Val Gly Xaa Cys Xaa Xaa Trp
1 5 10 15

Xaa

<210> 459
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 459

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

<210> 460
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 460

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

<210> 461
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 461

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

<210> 462
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 462

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

<210> 463
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 463

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

<210> 464
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 464

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

<210> 465
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 465

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

<210> 466
<211> 14
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 466

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

<210> 467
<211> 28
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 467

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

Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25

<210> 468
<211> 28
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 468

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

Gly Pro Thr Leu Arg Gln Cys Leu Ala Ala Arg Ala
20 25

<210> 469
<211> 9
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> misc_feature
<222> (6)..(8)
<223> Xaa=any amino acid

<400> 469

Val Arg Asp Gln Ile Xaa Xaa Xaa Leu
1 5

<210> 470
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 470

Thr Leu Arg Glu Trp Leu
1 5

<210> 471
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 471

Gly Arg Val Arg Asp Gln Val Ala Gly Trp
1 5 10

<210> 472
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 472

Gly Arg Val Lys Asp Gln Ile Ala Gln Leu
1 5 10

<210> 473
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 473

Gly Val Arg Asp Gln Val Ser Trp Ala Leu
1 5 10

<210> 474
<211> 10
<212> PRT
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<220>
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<400> 474

Glu Ser Val Arg Glu Gln Val Met Lys Tyr
1 5 10

<210> 475
<211> 10

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 475

Ser Val Arg Ser Gln Ile Ser Ala Ser Leu
1 5 10

<210> 476
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 476

Gly Val Arg Glu Thr Val Tyr Arg His Met
1 5 10

<210> 477
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 477

Gly Val Arg Glu Val Ile Val Met His Met Leu
1 5 10

<210> 478
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 478

Gly Arg Val Arg Asp Gln Ile Trp Ala Ala Leu
1 5 10

<210> 479
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 479

Ala Gly Val Arg Asp Gln Ile Leu Ile Trp Leu
1 5 10

<210> 480
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 480

Gly Arg Val Arg Asp Gln Ile Met Leu Ser Leu
1 5 10

<210> 481
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (8)..(10)
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<400> 481

Gly Arg Val Arg Asp Gln Ile Xaa Xaa Xaa Leu
1 5 10

<210> 482
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 482

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

<210> 483
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 483

Cys Thr Leu Gln Glu Phe Leu Glu Gly Cys
1 5 10

<210> 484
<211> 10
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 484

Cys Thr Arg Thr Glu Trp Leu His Gly Cys
1 5 10

<210> 485
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 485

Cys Thr Leu Arg Glu Trp Leu His Gly Gly Phe Cys
1 5 10

<210> 486
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 486

Cys Thr Leu Arg Glu Trp Val Phe Ala Gly Leu Cys
1 5 10

<210> 487
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 487

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

<210> 488
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 488

Cys Thr Leu Ala Glu Phe Leu Ala Ser Gly Val Glu Gln Cys
1 5 10

<210> 489
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 489

Cys Ser Leu Gln Glu Phe Leu Ser His Gly Gly Tyr Val Cys
1 5 10

<210> 490
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 490

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

<210> 491
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 491

Cys Thr Leu Lys Glu Trp Leu Val Ser His Glu Val Trp Cys
1 5 10

<210> 492
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (8)..(11)
<223> Xaa=any amino acid or nothing

<220>
<221> Misc_feature
<222> (12)..(13)
<223> Xaa=any amino acid

<400> 492

Cys Thr Leu Arg Glu Trp Leu Xaa Xaa Xaa Xaa Xaa Xaa Cys
1 5 10

<210> 493
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 493

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

<210> 494
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 494

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

<210> 495
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 495

Glu Arg Gly Pro Phe Trp Ala Lys Ala Cys
1 5 10

<210> 496
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 496

Arg Glu Gly Pro Arg Cys Val Met Trp Met
1 5 10

<210> 497
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 497

Cys Gly Thr Glu Gly Pro Thr Leu Ser Thr Trp Leu Asp Cys
1 5 10

<210> 498
<211> 14
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 498

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

<210> 499
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 499

Cys Glu Leu Val Gly Pro Ser Leu Met Ser Trp Leu Thr Cys
1 5 10

<210> 500
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 500

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

<210> 501
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 501

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

<210> 502
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 502

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

<210> 503

<211> 15
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Misc_feature
<222> (2)..(2)
<223> Xaa=any amino acid or nothing

<220>
<221> Misc_feature
<222> (3)..(3)
<223> Xaa=any amino acid

<220>
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<222> (13)..(13)
<223> Xaa=any amino acid or nothing

<220>
<221> Misc_feature
<222> (14)..(14)
<223> Xaa=any amino acid

<400> 503

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

<210> 504
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 504

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

<210> 505
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 505

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

Gly Gly

<210> 506
<211> 19
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 506

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

Pro Lys Asn

<210> 507
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 507

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

Arg Asp Thr

<210> 508
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 508

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

Thr Lys Lys

<210> 509
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 509

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

Thr Ser

<210> 510
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 510

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

Ala Ser

<210> 511
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 511

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

His Ser

<210> 512
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 512

Glu Glu Asp Cys Lys
1 5

<210> 513
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (1)..(5)
<223> Dimeric peptide

<400> 513

Glu Glu Asp Cys Lys

1 5

<210> 514
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (3)..(4)
<223> Non-amino acid moiety between residues 3 and 4

<400> 514

Glu Glu Asp Lys
1

<210> 515
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (1)..(5)
<223> Dimeric peptide

<220>
<221> Misc_feature
<222> (3)..(4)
<223> Non-amino acid moiety between residues 3 and 4

<400> 515

Glu Glu Asp Lys
1

<210> 516
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Phosphorylation
<222> (1)..(1)
<223> Phosphorylated Glu at position 1

<220>
<221> Misc_feature
<222> (3)..(4)
<223> Non-amino acid moiety between residues 3 and 4

<400> 516

Glu Glu Asp Lys
1

<210> 517
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Phosphorylation
<222> (1)..(1)
<223> Phosphorylated Glu at position 1

<220>
<221> Misc_feature
<222> (1)..(4)
<223> Dimeric peptide

<220>
<221> Misc_feature
<222> (3)..(4)
<223> Non-amino acid moiety between residues 3 and 4

<400> 517

Glu Glu Asp Lys
1

<210> 518
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (1)..(1)
<223> Pipecolic acid is before residue 1

<220>
<221> Misc_feature
<222> (2)..(3)
<223> Non-amino acid moiety between residues 2 and 3

<400> 518

Ser Asp Lys
1

<210> 519
<211> 3
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Pipecolic acid is before residue 1

<220>
<221> MISC_FEATURE
<222> (1)..(3)
<223> Dimeric peptide

<220>
<221> MISC_FEATURE
<222> (2)..(3)
<223> Non-amino acid moiety between residues 2 and 3

<400> 519

Ser Asp Lys
1

<210> 520
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (1)..(5)
<223> Dimeric peptide

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Non-amino acid moiety after residue 5

<400> 520

Glu Glu Asp Cys Lys
1 5

<210> 521
<211> 5
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> MISC_FEATURE
<222> (1)..(5)
<223> Dimeric peptide

<220>
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<222> (4)..(4)
<223> Xaa = any amino acid

<220>
<221> MISC_FEATURE

<222> (5)..(5)
<223> Non-amino acid moiety after residue 5

<400> 521

Glu Glu Asp Xaa Lys
1 5

<210> 522
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 522

Tyr Cys Phe Thr Ala Ser Glu Asn His Cys Tyr
1 5 10

<210> 523
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 523

Tyr Cys Phe Thr Asn Ser Glu Asn His Cys Tyr
1 5 10

<210> 524
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 524

Tyr Cys Phe Thr Arg Ser Glu Asn His Cys Tyr
1 5 10

<210> 525
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 525

Phe Cys Ala Ser Glu Asn His Cys Tyr
1 5

<210> 526
<211> 9
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 526

Tyr Cys Ala Ser Glu Asn His Cys Tyr
1 5

<210> 527
<211> 9
<212> PRT
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<220>
<223> Synthetic peptide

<400> 527

Phe Cys Asn Ser Glu Asn His Cys Tyr
1 5

<210> 528
<211> 9
<212> PRT
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<220>
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<400> 528

Phe Cys Asn Ser Glu Asn Arg Cys Tyr
1 5

<210> 529
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 529

Phe Cys Asn Ser Val Glu Asn Arg Cys Tyr
1 5 10

<210> 530
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 530

Tyr Cys Ser Gln Ser Val Ser Asn Asp Cys Phe
1 5 10

<210> 531

<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 531

Phe Cys Val Ser Asn Asp Arg Cys Tyr
1 5

<210> 532
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 532

Tyr Cys Arg Lys Glu Leu Gly Gln Val Cys Tyr
1 5 10

<210> 533
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 533

Tyr Cys Lys Glu Pro Gly Gln Cys Tyr
1 5

<210> 534
<211> 9
<212> PRT
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<220>
<223> Synthetic peptide

<400> 534

Tyr Cys Arg Lys Glu Met Gly Cys Tyr
1 5

<210> 535
<211> 9
<212> PRT
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<220>
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<400> 535

Phe Cys Arg Lys Glu Met Gly Cys Tyr
1 5

<210> 536
<211> 9
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<400> 546

Cys Ala Arg Arg Leu Asp Ala Pro Cys
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Cys Pro Ser Arg Leu Asp Ser Pro Cys
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Cys Asp Cys Arg Gly Asp Cys Phe Cys
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Cys Asp Cys Arg Gly Asp Cys Leu Cys
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<400> 552

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Xaa Xaa Xaa

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Cys Trp Asp Asp Leu Trp Trp Leu Cys
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Cys Trp Asp Asp Gly Trp Met Cys
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Cys Ser Trp Asp Asp Gly Trp Leu Cys
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Cys Pro Asp Asp Leu Trp Trp Leu Cys
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<400> 563

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1 5

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Asn Gly Arg Ala His Ala
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Cys Asn Gly Arg Cys
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<400> 569

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr Thr Leu

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<400> 575

Arg Asp Asp Leu His Met Leu Arg Leu Gln Leu Trp
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Ser Ser Asp Leu His Ala Leu Lys Lys Arg Tyr Gly
1 5 10

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<400> 577

Arg Gly Asp Leu Lys Gln Leu Ser Glu Leu Thr Trp
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<400> 578

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<400> 580

Asp Ile Thr Trp Asp Glu Leu Trp Lys Ile Met Asn
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1 5 10

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His Val Ser Trp Glu Gln Leu Trp Asp Ile Met Asn
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<210> 587
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<400> 588

Arg Asn Met Ser Trp Leu Glu Leu Trp Glu His Met Lys
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Ser Gln

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His Arg Ala Glu Trp Leu Ala Leu Trp Glu Gln Met Ser Pro
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Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys

1 5 10

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Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
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<210> 595
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<400> 596

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<210> 597
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<400> 597

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Asp

<210> 598
<211> 19
<212> PRT
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<400> 598

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Thr Asn Glu

<210> 599
<211> 13
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<400> 599

Lys Lys Ala Leu Thr Asn Glu Ala Glu Asn Trp Ala Asp
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<210> 601
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1 5 10 15

Thr Glu Glu

<210> 602
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<400> 602

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1 5 10 15

Asp

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<210> 604
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Thr Xaa Glu

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<210> 607
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<400> 607

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Thr Leu Leu Ser Ala Val Gly Ser Ala Leu Ser Ser Ser Gly Gly Gln
20 25 30

Gln

<210> 608
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<400> 608

Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe Lys
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Thr Leu Leu Ser Ala Val Gly Ser Ala Leu Ser Ser Ser Gly Gly Gln
20 25 30

Glu

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<220>
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<400> 609

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Thr Leu Leu Ser Ala Val
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<210> 610
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<400> 610

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Thr Leu Leu Ser Ala Val
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<400> 611

Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu Phe
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Lys Thr Leu Leu Ser Ala Val
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<210> 612
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Phe Lys Thr Leu Leu Ser Ala Val
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<210> 613
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<400> 613

Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
1 5 10 15

Phe Lys Thr Leu Leu Ser Ala Val
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<210> 614
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Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser
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<210> 615
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Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

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1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

<210> 617
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1 5 10 15

Ile Ser Trp Ile Lys Arg Lys Arg Gln Gln
20 25

<210> 618
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<400> 618

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1 5 10 15

Ile Ser Trp Ile Lys Arg
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Ile Lys Arg

<210> 620
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<210> 621
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1 5 10

<210> 622
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1 5 10

<210> 623
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<220>
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<400> 623

Lys Lys Leu Leu Lys Leu Lys Leu Lys Leu Lys Lys
1 5 10

<210> 624
<211> 12
<212> PRT
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<220>
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<400> 624

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 625
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 625

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 626
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 626

Lys Leu Leu Leu Leu Lys
1 5

<210> 627
<211> 8
<212> PRT
<213> Artificial sequence

<220>
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<400> 627

Lys Leu Leu Leu Lys Leu Leu Lys
1 5

<210> 628
<211> 12
<212> PRT
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<220>
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<400> 628

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 629
<211> 12
<212> PRT
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<220>
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<400> 629

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 630
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 630

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys
1 5 10

<210> 631
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<220>
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<400> 631

Lys Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Lys
1 5 10

<210> 632
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 632

Lys Val Val Val Lys Val Val Val Lys Val Val Lys
1 5 10

<210> 633
<211> 12
<212> PRT
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<220>
<223> Synthetic peptide

<400> 633

Lys Val Val Val Lys Val Lys Val Lys Val Val Lys
1 5 10

<210> 634
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 634

Lys Val Val Val Lys Val Lys Val Lys Val Lys
1 5 10

<210> 635
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 635

Lys Val Val Val Lys Val Lys Val Lys Val Val Lys
1 5 10

<210> 636
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 636

Lys Leu Ile Leu Lys Leu
1 5

<210> 637
<211> 6
<212> PRT
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<220>
<223> Synthetic peptide

<400> 637

Lys Val Leu His Leu Leu
1 5

<210> 638
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 638

Leu Lys Leu Arg Leu Leu
1 5

<210> 639
<211> 6
<212> PRT
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<220>
<223> Synthetic peptide

<400> 639

Lys Pro Leu His Leu Leu
1 5

<210> 640
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 640

Lys Leu Ile Leu Lys Leu Val Arg
1 5

<210> 641
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 641

Lys Val Phe His Leu Leu His Leu
1 5

<210> 642
<211> 8
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 642

His Lys Phe Arg Ile Leu Lys Leu
1 5

<210> 643
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 643

Lys Pro Phe His Ile Leu His Leu
1 5

<210> 644
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 644

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 645
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 645

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 646
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 646

Lys Ile Ile Ile Lys Ile Lys Ile Lys Ile Ile Lys
1 5 10

<210> 647
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 647

Lys Ile Pro Ile Lys Ile Lys Ile Lys Ile Pro Lys
1 5 10

<210> 648
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 648

Lys Ile Pro Ile Lys Ile Lys Ile Lys Ile Val Lys
1 5 10

<210> 649
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 649

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

<210> 650
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 650

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

<210> 651
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 651

Arg Ile Ile Ile Arg Ile Arg Ile Arg Ile Ile Arg
1 5 10

<210> 652
<211> 12

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 652

Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg
1 5 10

<210> 653
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 653

Arg Ile Ile Val Arg Ile Arg Leu Arg Ile Ile Arg
1 5 10

<210> 654
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 654

Arg Ile Gly Ile Arg Leu Arg Val Arg Ile Ile Arg
1 5 10

<210> 655
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 655

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg
1 5 10

<210> 656
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 656

Arg Ile Ala Val Lys Trp Arg Leu Arg Phe Ile Lys
1 5 10

<210> 657
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 657

Lys Ile Gly Trp Lys Leu Arg Val Arg Ile Ile Arg
1 5 10

<210> 658
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 658

Lys Lys Ile Gly Trp Leu Ile Ile Arg Val Arg Arg
1 5 10

<210> 659
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 659

Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg
1 5 10

<210> 660
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 660

Arg Ile Ile Val Arg Ile Arg Leu Arg Ile Ile Arg Val Arg
1 5 10

<210> 661
<211> 14
<212> PRT
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<220>
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<400> 661

Arg Ile Gly Ile Arg Leu Arg Val Arg Ile Ile Arg Arg Val
1 5 10

<210> 662
<211> 16
<212> PRT
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<220>
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<400> 662

Lys Ile Val Ile Arg Ile Arg Ala Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

<210> 663
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 663

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 664
<211> 16
<212> PRT
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<220>
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<400> 664

Lys Ile Gly Ile Lys Ala Arg Val Arg Ile Ile Arg Val Lys Ile Ile
1 5 10 15

<210> 665
<211> 16
<212> PRT
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<220>
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<400> 665

Arg Ile Ile Val His Ile Arg Leu Arg Ile Ile His His Ile Arg Leu
1 5 10 15

<210> 666
<211> 16
<212> PRT
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<220>
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<400> 666

His Ile Gly Ile Lys Ala His Val Arg Ile Ile Arg Val His Ile Ile
1 5 10 15

<210> 667
<211> 16
<212> PRT
<213> Artificial sequence

<220>
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<400> 667

Arg Ile Tyr Val Lys Ile His Leu Arg Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 668
<211> 16
<212> PRT
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<220>
<223> Synthetic peptide

<400> 668

Lys Ile Gly His Lys Ala Arg Val His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 669
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 669

Arg Ile Tyr Val Lys Pro His Pro Arg Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 670
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 670

Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 671
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 671

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

Lys Ile Val

<210> 672
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 672

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

Ile Lys Lys

<210> 673
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 673

Lys Ile Gly Trp Lys Leu Arg Val Arg Ile Ile Arg Val Lys Ile Gly
1 5 10 15

Arg Leu Arg

<210> 674
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 674

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

Lys Ile Val Lys Val Lys Arg Ile Arg
20 25

<210> 675
<211> 26
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 675

Arg Phe Ala Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

Ile Lys Lys Ile Arg Lys Arg Val Ile Lys
20 25

<210> 676
<211> 30
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 676

Lys Ala Gly Trp Lys Leu Arg Val Arg Ile Ile Arg Val Lys Ile Gly
1 5 10 15

Arg Leu Arg Lys Ile Gly Trp Lys Lys Arg Val Arg Ile Lys
20 25 30

<210> 677
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 677

Arg Ile Tyr Val Lys Pro His Pro Arg Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 678
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 678

Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile Ile
1 5 10 15

<210> 679
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 679

Lys Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Ile Arg
1 5 10 15

Lys Ile Val

<210> 680
<211> 19
<212> PRT
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<220>
<223> Synthetic peptide

<400> 680

Arg Ile Ile Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg Leu
1 5 10 15

Ile Lys Lys

<210> 681
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 681

Arg Ile Tyr Val Ser Lys Ile Ser Ile Tyr Ile Lys Lys Ile Arg Leu
1 5 10 15

<210> 682
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 682

Lys Ile Val Ile Phe Thr Arg Ile Arg Leu Thr Ser Ile Arg Ile Arg
1 5 10 15

Ser Ile Val

<210> 683
<211> 16
<212> PRT
<213> Artificial sequence

<220>
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<400> 683

Lys Pro Ile His Lys Ala Arg Pro Thr Ile Ile Arg Tyr Lys Met Ile
1 5 10 15

<210> 684
<211> 25
<212> PRT
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<220>
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<400> 684

Cys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro Leu
1 5 10 15

Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 685
<211> 26
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 685

Cys Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser Pro
1 5 10 15

Leu Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 686
<211> 27
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 686

Cys Lys Lys Lys Gly Phe Phe Ala Leu Ile Pro Lys Ile Ile Ser Ser
1 5 10 15

Pro Leu Phe Lys Thr Leu Leu Ser Ala Val Cys
20 25

<210> 687
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 687

Cys Arg Ile Val Ile Arg Ile Arg Ile Arg Leu Ile Arg Ile Arg Cys
1 5 10 15

<210> 688
<211> 18
<212> PRT
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<220>
<223> Synthetic peptide

<400> 688

Cys Lys Pro Gly His Lys Ala Arg Pro His Ile Ile Arg Tyr Lys Ile
1 5 10 15

Ile Cys

<210> 689
<211> 28
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 689

Cys Arg Phe Ala Val Lys Ile Arg Leu Arg Ile Ile Lys Lys Ile Arg
1 5 10 15

Leu Ile Lys Lys Ile Arg Lys Arg Val Ile Lys Cys
20 25

<210> 690
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 690

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys Cys
1 5 10

<210> 691
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 691

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 692
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 692

Lys Leu Leu Leu Lys Leu Lys Leu Lys Leu Leu Lys Cys
1 5 10

<210> 693
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 693

Lys Leu Leu Leu Lys Leu Leu Leu Lys Leu Leu Lys
1 5 10

<210> 694
<211> 28
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 694

His Ser Asp Ala Val Phe Tyr Asp Asn Tyr Thr Arg Leu Arg Lys Gln
1 5 10 15

Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
20 25

<210> 695
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa=Norleucine

<400> 695

Xaa His Ser Asp Ala Val Phe Tyr Asp Asn Tyr Thr Arg Leu Arg Lys
1 5 10 15

Gln Met Ala Val Lys Lys Tyr Leu Asn Ser Ile Leu Asn
20 25

<210> 696
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (1)..(1)
<223> Xaa=Ala, Val, Lys, D-Lys, Orn, or nothing

<220>
<221> Misc_feature
<222> (2)..(2)
<223> If residue 1 is Ala, Xaa=Val or nothing; if residue 1 is Val, Xaa=Ala, Lys or nothing; if residue 1 not Ala or Val, Xaa=nothing

<220>
<221> Misc_feature
<222> (3)..(3)
<223> If residue 2 is Val or Ala, Xaa=Lys or nothing; if residue 2 is not Val or Ala, Xaa=nothing

<220>
<221> Misc_feature
<222> (4)..(4)
<223> Xaa=L-Lys, D-Lys, or Orn

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=L-Tyr, D-Tyr, Phe, Trp, or p-amino phenylalanine

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=Ala, D-Ala, Ile, D-Ile, Leu, D-Leu, Met, D-Met, Val, D-Val, Nva, D-Nva, Nle, or D-Nle

<220>
<221> Misc_feature
<222> (7)..(7)
<223> Xaa=Asn, Ser, Ile, Tyr, Leu, D-Ala, Nle, or nothing

<220>
<221> Misc_feature
<222> (8)..(8)
<223> If residue 7 is Asn, Xaa=Ser or nothing; if residue 7 is not Asn, Xaa=nothing

<220>
<221> Misc_feature
<222> (9)..(9)
<223> If residue 8 is Ser, Xaa=Ile, Tyr, or nothing; if residue 8 is not Ser, Xaa=nothing

<220>
<221> Misc_feature
<222> (10)..(10)
<223> If residue 9 is Ile or Tyr, Xaa=Leu; if residue 9 is not Ile or Tyr, Xaa=nothing

<220>
<221> Misc_feature
<222> (11)..(11)
<223> If residue 10 is Leu, Xaa=Asn; if residue 10 is not Leu, Xaa=nothing

<400> 696

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 697
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<220>
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<222> (1)..(4)
<223> Xaa=Asn, Ala, D-Ala, Ile, D-Ile, Leu, D-Leu, Met, D-Met, Val, D-Val, Nva, D-Nva, Nle, D-Nle, Tyr, Lys, or nothing

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Asn, Ala, D-Ala, Ile, D-Ile, Leu, D-Leu, Met, D-Met, Val, D-Val, Nva, D-Nva, Nle, D-Nle, Tyr, or nothing

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=Ala, D-Ala, Ile, D-Ile, Leu, D-Leu, Met, D-Met, Val, D-Val, Nva, D-Nva, Nle, D-Nle, or nothing

<220>
<221> Misc_feature
<222> (7)..(7)
<223> Xaa=Asn or nothing

<220>
<221> Misc_feature
<222> (9)..(9)
<223> Xaa=Ile or Tyr

<400> 697

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ser Xaa Leu Asn
1 5 10

<210> 698

<400> 698
000

<210> 699
<211> 4
<212> PRT
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<220>
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<400> 699

Lys Lys Tyr Leu
1

<210> 700
<211> 5
<212> PRT
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<220>
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<400> 700

Asn Ser Ile Leu Asn
1 5

<210> 701
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 701

Lys Lys Tyr Leu
1

<210> 702
<211> 4
<212> PRT
<213> Artificial sequence

<220>
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<400> 702

Lys Lys Tyr Ala
1

<210> 703
<211> 6
<212> PRT
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<220>
<223> Synthetic peptide

<400> 703

Ala Val Lys Lys Tyr Leu
1 5

<210> 704
<211> 5
<212> PRT
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<220>
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<400> 704

Asn Ser Ile Leu Asn
1 5

<210> 705
<211> 4
<212> PRT
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<220>
<223> Synthetic peptide

<400> 705

Lys Lys Tyr Val
1

<210> 706
<211> 3
<212> PRT
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<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (2)..(3)
<223> A lauroyl moiety is between residues 2 and 3

<400> 706

Ser Ile Asn
1

<210> 707
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (5)..(5)
<223> Xaa=Norleucine

<400> 707

Lys Lys Tyr Leu Xaa
1 5

<210> 708
<211> 5
<212> PRT
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<220>
<223> Synthetic peptide

<400> 708

Asn Ser Tyr Leu Asn
1 5

<210> 709
<211> 5
<212> PRT
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<220>
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<400> 709

Asn Ser Ile Tyr Asn
1 5

<210> 710
<211> 11
<212> PRT
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<220>
<223> Synthetic peptide

<400> 710

Lys Lys Tyr Leu Pro Pro Asn Ser Ile Leu Asn
1 5 10

<210> 711
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (1)..(1)
<223> A lauroyl moiety is bound to residue 1

<400> 711

Lys Lys Tyr Leu
1

<210> 712
<211> 4
<212> PRT
<213> Artificial sequence

<220>
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<220>
<221> Binding
<222> (1)..(1)
<223> A caproyl moiety is bound to residue 1

<400> 712

Lys Lys Tyr Leu
1

<210> 713
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 713

Lys Tyr Leu
1

<210> 714
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (4)..(4)
<223> Xaa=Norleucine

<400> 714

Lys Lys Tyr Xaa
1

<210> 715
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 715

Val Lys Lys Tyr Leu
1 5

<210> 716
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 716

Leu Asn Ser Ile Leu Asn
1 5

<210> 717
<211> 7
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 717

Tyr Leu Asn Ser Ile Leu Asn
1 5

<210> 718
<211> 5
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Lys Lys Tyr Leu Asn Ser Ile Leu

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Lys Lys Tyr Asp Ala
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Ala Val Lys Lys Tyr Leu
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Cys Lys Lys Tyr Leu Cys

1 5

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Cys Lys Lys Tyr Leu Lys
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Lys Lys Tyr Ala
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1 5 10

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Thr Phe Ser Asp Leu Trp
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1 5 10 15

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Pro Ala Phe Ser Arg Phe Trp Ser Asp Leu Ser Ala Gly Ala His
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Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
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Gln Pro Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro
1 5 10

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1 5 10

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Gln Pro Thr Phe Ser Asp Tyr Trp Lys Leu Leu Pro
1 5 10

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

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Ser Cys Trp Lys Tyr Trp Gly Lys Glu Cys Gly Ser
1 5 10

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Ser Cys Tyr Glu Trp Gly Lys Leu Arg Trp Cys Gly Ser
1 5 10

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1 5 10

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1 5 10

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1 5 10

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1 5 10

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1 5 10

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1 5 10

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Thr Met Leu Ala Lys

20

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1 5 10 15

Lys Lys

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1 5 10 15

Ser Ser

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1 5 10

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1 5 10 15

Val Ala

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1 5 10

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1 5 10 15

Leu Leu

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1 5 10 15

Val

<210> 812
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1 5 10 15

Ser

<210> 813
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1 5 10 15

Thr

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1 5 10 15

Asn

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1 5 10

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1 5 10 15

Arg

<210> 817
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1 5 10 15

Thr

<210> 818
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Gly Ser Gly Ser Tyr Asp Thr Leu Ala Leu Pro Ser Leu Pro Leu His
1 5 10 15

Pro Met Ser Ser
20

<210> 819
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1 5 10 15

Pro Met Ser Ser
20

<210> 820
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Gly Ser Gly Ser Ser Gly Val Thr Met Tyr Pro Lys Leu Pro Pro His

1 5 10 15

Trp Ser Met Ala
20

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Gly Ser Gly Ser Ser Gly Val Arg Met Tyr Pro Lys Leu Pro Pro His
1 5 10 15

Trp Ser Met Ala
20

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1 5 10 15

Ala Lys His Gly
20

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Arg Asn Arg Gln

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Arg Gln Lys Thr
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Ser Pro Leu Pro Pro Leu Pro
1 5

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1 5

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Arg Gln Leu Pro Pro Thr Pro
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Arg Pro Leu Pro Ser Arg Pro
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Arg Pro Leu Pro Thr Arg Pro
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Arg Ala Leu Pro Ser Pro Pro
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Arg Pro Val Pro Pro Ile Thr
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Pro Pro Pro Tyr Pro Pro Pro Pro Ile Pro Xaa Xaa
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<400> 861

Xaa Xaa Xaa Arg Pro Leu Pro Xaa Leu Pro

1 5 10

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<223> Xaa=Phe, Tyr, or Trp

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<223> Xaa=any amino acid

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<400> 862

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<400> 863

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<210> 864
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<223> Xaa=His, Lys, or Arg

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<400> 864

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1 5 10

<210> 865
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<400> 865

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<400> 866

Xaa Pro Xaa Leu Pro Xaa Lys
1 5

<210> 867
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<223> Xaa=any amino acid

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<400> 867

Xaa Xaa Asp Xaa Pro Leu Pro Xaa Leu Pro
1 5 10

<210> 868
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<212> PRT
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<222> (1)..(1)
<223> Xaa=Asp, Arg, Met, Pro, or Cys

<220>
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<222> (2)..(2)
<223> If residue 1 is Asp, Xaa=Arg; if residue 1 is Arg, Xaa=Met; if residue 1 is Met, Xaa=Pro; if residue 1 is Pro, Xaa=Cys; if residue 1 is Cys, Xaa=nothing

<220>
<221> Misc_feature
<222> (3)..(3)
<223> If residue 1 is Asp, Xaa=Met; if residue 1 is Arg, Xaa=Pro; if residue 1 is Met, Xaa=Cys; if residue 1 is Pro or Cys, Xaa=nothing

<220>
<221> Misc_feature
<222> (4)..(4)
<223> If residue 1 is Asp, Xaa=Pro; if residue 1 is Arg, Xaa=Cys; if residue 1 is Met, Pro, or Cys, Xaa=nothing

<220>
<221> Misc_feature
<222> (5)..(5)
<223> If residue 1 is Asp, Xaa=Cys; if residue 1 is Arg, Met, Pro, or Cys, Xaa=nothing

<220>
<221> Misc_feature
<222> (6)..(6)
<223> Xaa=Arg or Lys

<220>
<221> Misc_feature
<222> (14)..(14)
<223> Xaa=Ser or Thr

<220>
<221> Misc_feature
<222> (16)..(16)
<223> Xaa=Cys

<220>
<221> Misc_feature
<222> (17)..(17)
<223> Xaa=Lys or nothing

<400> 868

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1 5 10 15

Xaa

<210> 869
<211> 17
<212> PRT
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<220>
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<400> 869

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15

Lys

<210> 870
<211> 15
<212> PRT
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<220>
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<400> 870

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10 15

<210> 871
<211> 13
<212> PRT
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<220>
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<400> 871

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10

<210> 872
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<212> PRT
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<400> 872

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15

<210> 873
<211> 14
<212> PRT
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<400> 873

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 874
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<212> PRT
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<400> 874

Cys Arg Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 875
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<400> 875

Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10 15

<210> 876
<211> 15
<212> PRT
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<400> 876

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10 15

<210> 877
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<212> PRT
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<220>
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Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys Lys
1 5 10

<210> 878
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<212> PRT
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Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys

1 5 10 15

<210> 879
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<212> PRT
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Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 880
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Cys Lys Asn Phe Phe Trp Lys Thr Phe Ser Ser Cys
1 5 10

<210> 881
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<212> PRT
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<220>
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<400> 881

Asp Arg Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

Lys

<210> 882
<211> 15
<212> PRT
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<220>
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<400> 882

Met Pro Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10 15

<210> 883
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<400> 883

Cys Arg Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10

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1 5 10 15

<210> 885
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1 5 10

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1 5 10

<210> 887
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Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

Lys

<210> 888
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<400> 888

Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
1 5 10 15

<210> 889
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Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys Lys
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Asp Arg Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10 15

<210> 891
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Met Pro Cys Lys Asn Phe Phe Trp Lys Thr Phe Thr Ser Cys
1 5 10

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

1 5 10

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Thr

<210> 894
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<400> 894

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

Phe

<210> 895
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Arg

<210> 896
<211> 17
<212> PRT
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<400> 896

Ala Glu Ser Ser Leu Trp Thr Arg Tyr Ala Trp Pro Ser Met Pro Ser

1 5 10 15

Tyr

<210> 897
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<212> PRT
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Ala Glu Trp His Pro Gly Leu Ser Phe Gly Ser Tyr Leu Trp Ser Lys
1 5 10 15

Thr

<210> 898
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1 5 10 15

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<210> 899
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Phe

<210> 900
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<400> 900

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Met

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1 5 10 15

Gly

<210> 902
<211> 17
<212> PRT
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<400> 902

Ala Glu Ile Ser Phe Ser Glu Leu Met Trp Leu Arg Ser Thr Pro Ala
1 5 10 15

Phe

<210> 903
<211> 17
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<400> 903

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Ser

<210> 904
<211> 17
<212> PRT

<213> Artificial sequence

<220>
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<400> 904

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Ser

<210> 905
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<212> PRT
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<220>
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<400> 905

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

Val

<210> 906
<211> 17
<212> PRT
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<220>
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<400> 906

Ala Glu Thr Leu Phe Met Asp Leu Trp His Asp Lys His Ile Leu Leu
1 5 10 15

Thr

<210> 907
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<212> PRT
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<220>
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<400> 907

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

Glu

<210> 908
<211> 17
<212> PRT
<213> Artificial sequence

<220>
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<400> 908

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

Arg

<210> 909
<211> 17
<212> PRT
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<220>
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<400> 909

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

Tyr

<210> 910
<211> 17
<212> PRT
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<220>
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<400> 910

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1 5 10 15

Thr

<210> 911
<211> 17
<212> PRT
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<220>
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<400> 911

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1 5 10 15

Ala

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1 5 10

<210> 913
<211> 17
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<400> 913

Ala Glu Ser Thr Tyr His His Leu Ser Leu Gly Tyr Met Tyr Thr Leu
1 5 10 15

Asn

<210> 914
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<400> 914

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1 5 10

<210> 915
<211> 19
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<400> 915

Val Glu Pro Asn Cys Asp Ile His Val Met Trp Glu Trp Glu Cys Phe
1 5 10 15

Glu Arg Leu

<210> 916
<211> 18
<212> PRT
<213> Artificial sequence

<220>
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<400> 916

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

Glu Ser

<210> 917
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 917

Arg Gly Trp Val Glu Ile Cys Val Ala Asp Asp Asn Gly Met Cys Val
1 5 10 15

Thr Glu Ala Gln
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<210> 918
<211> 19
<212> PRT
<213> Artificial sequence

<220>
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<400> 918

Gly Trp Asp Glu Cys Asp Val Ala Arg Met Trp Glu Trp Glu Cys Phe
1 5 10 15

Ala Gly Val

<210> 919
<211> 18
<212> PRT
<213> Artificial sequence

<220>
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<400> 919

Gly Glu Arg Trp Cys Phe Asp Gly Pro Arg Ala Trp Val Cys Gly Trp
1 5 10 15

Glu Ile

<210> 920
<211> 18
<212> PRT
<213> Artificial sequence

<220>
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<400> 920

Glu Glu Leu Trp Cys Phe Asp Gly Pro Arg Ala Trp Val Cys Gly Tyr
1 5 10 15

Val Lys

<210> 921
<211> 20
<212> PRT
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<220>
<223> Synthetic peptide

<400> 921

Arg Gly Trp Val Glu Ile Cys Ala Ala Asp Asp Tyr Gly Arg Cys Leu
1 5 10 15

Thr Glu Ala Gln
20

<210> 922
<211> 16
<212> PRT
<213> Artificial sequence

<220>
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<400> 922

Arg Gly Trp Val Glu Ile Cys Glu Ser Asp Val Trp Gly Arg Cys Leu
1 5 10 15

<210> 923
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 923

Arg Gly Trp Val Glu Ile Cys Glu Ser Asp Val Trp Gly Arg Cys Leu
1 5 10 15

<210> 924
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 924

Gly Gly Asn Glu Cys Asp Ile Ala Arg Met Trp Glu Trp Glu Cys Phe
1 5 10 15

Glu Arg Leu

<210> 925
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 925

Arg Gly Trp Val Glu Ile Cys Ala Ala Asp Asp Tyr Gly Arg Cys Leu
1 5 10 15

<210> 926
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 926

Cys Thr Thr His Trp Gly Phe Thr Leu Cys
1 5 10

<210> 927
<211> 8
<212> PRT
<213> Artificial sequence

<220>
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<223> Xaa=any amino acid

<400> 927

Cys Leu Arg Ser Gly Xaa Gly Cys
1 5

<210> 928
<211> 10
<212> PRT
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<220>
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<223> Xaa=any amino acid

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<223> Xaa=any amino acid

<400> 928

Cys Xaa Xaa His Trp Gly Phe Xaa Xaa Cys
1 5 10

<210> 929
<211> 5
<212> PRT
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<220>
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<222> (2)..(2)
<223> Xaa= any amino acid

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<221> Misc_feature
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<223> Xaa= any amino acid

<400> 929

Cys Xaa Pro Xaa Cys
1 5

<210> 930
<211> 10

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 930

Cys Arg Arg His Trp Gly Phe Glu Phe Cys
1 5 10

<210> 931
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 931

Ser Thr Thr His Trp Gly Phe Thr Leu Ser
1 5 10

<210> 932
<211> 10
<212> PRT
<213> Artificial sequence

<220>
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<400> 932

Cys Ser Leu His Trp Gly Phe Trp Trp Cys
1 5 10

<210> 933
<211> 15
<212> PRT
<213> Artificial sequence

<220>
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<400> 933

Gly Phe Val Cys Ser Gly Ile Phe Ala Val Gly Val Gly Arg Cys
1 5 10 15

<210> 934
<211> 15
<212> PRT
<213> Artificial sequence

<220>
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<400> 934

Ala Pro Gly Val Arg Leu Gly Cys Ala Val Leu Gly Arg Tyr Cys
1 5 10 15

<210> 935
<211> 6
<212> PRT
<213> Artificial sequence

<220>
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<400> 935

Leu Leu Gly Arg Met Lys
1 5

<210> 936
<211> 27
<212> PRT
<213> Artificial sequence

<220>
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<400> 936

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

Met Ala Asn Leu Thr Ser His Ala Ser Ala Ile
20 25

<210> 937
<211> 13
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<220>
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<400> 937

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

<210> 938
<211> 11
<212> PRT
<213> Artificial sequence

<220>
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<400> 938

Cys Val Val Gln Asp Trp Gly His His Ala Cys
1 5 10

<210> 939
<211> 27
<212> PRT
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<220>
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<400> 939

Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Gly Val Ser
1 5 10 15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
20 25

<210> 940
<211> 27
<212> PRT
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<220>
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<400> 940

Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Arg Val Ser
1 5 10 15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
20 25

<210> 941
<211> 30
<212> PRT
<213> Artificial sequence

<220>
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<400> 941

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

Met Lys Glu Ala Ser Asn Val Phe Pro Ser Arg Arg Ser Arg
20 25 30

<210> 942
<211> 30
<212> PRT
<213> Artificial sequence

<220>
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<400> 942

Ser Ser Gln Asn Trp Asp Met Glu Ala Gly Val Glu Asp Leu Thr Ala
1 5 10 15

Ala Met Leu Gly Leu Leu Ser Thr Ile His Ser Ser Ser Arg
20 25 30

<210> 943
<211> 31
<212> PRT
<213> Artificial sequence

<220>
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<400> 943

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

Ala Thr Arg Ile Gln Asp Leu Leu Ile Ala Ser Arg Pro Ser Arg
20 25 30

<210> 944
<211> 31
<212> PRT
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<220>
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<400> 944

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

Asp Ala Thr Arg Thr Ser Ile Pro Pro Ser Leu Gln Asn Ser Arg
20 25 30

<210> 945
<211> 18
<212> PRT
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<220>
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<400> 945

Asp Val Tyr Thr Lys Lys Glu Leu Ile Glu Cys Ala Arg Arg Val Ser
1 5 10 15

Glu Lys

<210> 946
<211> 22
<212> PRT
<213> Artificial sequence

<220>
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<400> 946

Glu Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala Gln Phe His Ile
1 5 10 15

Asp Tyr Asn Asn Val Ser
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<210> 947
<211> 22
<212> PRT
<213> Artificial sequence

<220>
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<400> 947

Ser Gly Ile Ala Gln Phe His Ile Asp Tyr Asn Asn Val Ser Ser Ala
1 5 10 15

Glu Gly Trp His Val Asn
20

<210> 948
<211> 34
<212> PRT
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<220>
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<400> 948

Leu Val Thr Val Glu Lys Gly Ser Tyr Tyr Pro Gly Ser Gly Ile Ala
1 5 10 15

Gln Phe His Ile Asp Tyr Asn Asn Val Ser Ser Ala Glu Gly Trp His
20 25 30

Val Asn

<210> 949
<211> 14
<212> PRT
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<220>
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<400> 949

Ser Gly Ile Ala Gln Phe His Ile Asp Tyr Asn Asn Val Ser
1 5 10

<210> 950
<211> 6
<212> PRT
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<220>
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<400> 950

Leu Leu Gly Arg Met Lys
1 5

<210> 951
<211> 8
<212> PRT
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<220>
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<400> 951

Ala Leu Leu Gly Arg Met Lys Gly
1 5

<210> 952
<211> 6
<212> PRT
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<220>
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<400> 952

Leu Asp Pro Ala Phe Arg
1 5

<210> 953
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<212> PRT
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<220>
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<220>
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<223> Xaa=any amino acid

<400> 953

Cys Xaa Xaa Arg Gly Asp Cys
1 5

<210> 954
<211> 7
<212> PRT
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<220>
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<400> 954

Arg Pro Leu Pro Pro Leu Pro
1 5

<210> 955
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<220>

<223> Synthetic peptide

<400> 955

Pro Pro Val Pro Pro Arg
1 5

<210> 956
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<223> Xaa= any amino acid

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<400> 956

Xaa Phe Xaa Asp Xaa Trp Xaa Xaa Leu Xaa Xaa
1 5 10

<210> 957
<211> 20
<212> PRT
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<220>
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<400> 957

Lys Ala Cys Arg Arg Leu Phe Gly Pro Val Asp Ser Glu Gln Leu Ser
1 5 10 15

Arg Asp Cys Asp
20

<210> 958
<211> 20

<212> PRT
<213> Artificial sequence

<220>
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<400> 958

Arg Glu Arg Trp Asn Phe Asp Phe Val Thr Glu Thr Pro Leu Glu Gly
1 5 10 15

Asp Phe Ala Trp
20

<210> 959
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 959

Lys Arg Arg Gln Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg
1 5 10 15

Leu Ile Phe Ser
20

<210> 960
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 960

Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg Leu Ile Phe Ser
1 5 10 15

Lys Arg Lys Pro
20

<210> 961
<211> 5
<212> PRT
<213> Artificial sequence

<220>
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<400> 961

Arg Arg Leu Ile Phe
1 5

<210> 962
<211> 36

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 962

Lys Arg Arg Gln Thr Ser Ala Thr Asp Phe Tyr His Ser Lys Arg Arg
1 5 10 15

Leu Ile Phe Ser Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met
20 25 30

Lys Trp Lys Lys
35

<210> 963
<211> 24
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 963

Lys Arg Arg Leu Ile Phe Ser Lys Arg Gln Ile Lys Ile Trp Phe Gln
1 5 10 15

Asn Arg Arg Met Lys Trp Lys Lys
20

<210> 964
<211> 24
<212> PRT
<213> Artificial sequence

<220>
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<400> 964

Asn Gln Gly Arg His Phe Cys Gly Ala Leu Ile His Ala Arg Phe Val
1 5 10 15

Met Thr Ala Ala Ser Cys Phe Gln
20

<210> 965
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 965

Arg His Phe Cys Gly Gly Ala Leu Ile His Ala Arg Phe Val Met Thr
1 5 10 15

Ala Ala Ser Cys
20

<210> 966
<211> 27
<212> PRT
<213> Artificial sequence

<220>
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<400> 966

Gly Thr Arg Cys Gln Val Ala Gly Trp Gly Ser Gln Arg Ser Gly Gly
1 5 10 15

Arg Leu Ser Arg Phe Pro Arg Phe Val Asn Val
20 25

<210> 967
<211> 15
<212> PRT
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<400> 967

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

<210> 968
<211> 6
<212> PRT
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<220>
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<400> 968

Leu Lys Thr Pro Arg Val
1 5

<210> 969
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<212> PRT
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<220>
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<400> 969

Asn Thr Leu Lys Thr Pro Arg Val
1 5

<210> 970
<211> 11

<212> PRT
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<220>
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<400> 970

Asn Thr Leu Lys Thr Pro Arg Val Gly Gly Cys
1 5 10

<210> 971
<211> 6
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<220>
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<400> 971

Lys Asp Lys Ala Thr Phe
1 5

<210> 972
<211> 10
<212> PRT
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<220>
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<400> 972

Lys Asp Lys Ala Thr Phe Gly Cys His Asp
1 5 10

<210> 973
<211> 12
<212> PRT
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<400> 973

Lys Asp Lys Ala Thr Phe Gly Cys His Asp Gly Cys
1 5 10

<210> 974
<211> 6
<212> PRT
<213> Artificial sequence

<220>
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<400> 974

Thr Leu Arg Val Tyr Lys
1 5

<210> 975
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<212> PRT
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<220>
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<400> 975

Ala Thr Leu Arg Val Tyr Lys Gly Gly
1 5

<210> 976
<211> 10
<212> PRT
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<220>
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<400> 976

Cys Ala Thr Leu Arg Val Tyr Lys Gly Gly
1 5 10

<210> 977
<211> 14
<212> PRT
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<220>
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<400> 977

Ile Asn Leu Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
1 5 10

<210> 978
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 978

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly
1 5 10

<210> 979
<211> 27
<212> PRT
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<220>
<223> Synthetic peptide

<400> 979

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Lys Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 980
<211> 7
<212> PRT
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<220>
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<400> 980

Cys Val His Ala Tyr Arg Ser
1 5

<210> 981
<211> 7
<212> PRT
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<220>
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<400> 981

Cys Val His Ala Tyr Arg Ala
1 5

<210> 982
<211> 7
<212> PRT
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<220>
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<400> 982

Cys Val His Ala Pro Arg Ser
1 5

<210> 983
<211> 7
<212> PRT
<213> Artificial sequence

<220>
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<400> 983

Cys Val His Ala Pro Arg Ala
1 5

<210> 984
<211> 7
<212> PRT
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<220>

<223> Synthetic peptide

<400> 984

Cys Val His Ser Tyr Arg Ser
1 5

<210> 985
<211> 7
<212> PRT
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<220>
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<400> 985

Cys Val His Ser Tyr Arg Ala
1 5

<210> 986
<211> 7
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<220>
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<400> 986

Cys Val His Ser Pro Arg Ser
1 5

<210> 987
<211> 7
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<220>
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<400> 987

Cys Val His Ser Pro Arg Ala
1 5

<210> 988
<211> 7
<212> PRT
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<220>
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<400> 988

Cys Val His Thr Tyr Arg Ser
1 5

<210> 989
<211> 7
<212> PRT
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<220>
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<400> 989

Cys Val His Thr Tyr Arg Ala
1 5

<210> 990
<211> 7
<212> PRT
<213> Artificial sequence

<220>
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<400> 990

Cys Val His Thr Pro Arg Ser
1 5

<210> 991
<211> 7
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<220>
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<400> 991

Cys Val His Thr Pro Arg Ala
1 5

<210> 992
<211> 6
<212> PRT
<213> Artificial sequence

<220>
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<400> 992

His Trp Ala Trp Phe Lys
1 5

<210> 993
<211> 32
<212> PRT
<213> Artificial sequence

<220>
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<400> 993

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

Asn Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25 30

<210> 994
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 994

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu
20 25 30

Ala Ala Arg Ala
35

<210> 995
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 995

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu
20 25 30

Ala Ala Arg Ala
35

<210> 996
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 996

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Ala Leu
20 25 30

Ala Ala Arg Ala
35

<210> 997
<211> 36
<212> PRT
<213> Artificial sequence

<220>
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<400> 997

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

Gly Lys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 998
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 998

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

Gly Lys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 999
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 999

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

Gly Cys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1000
<211> 36

<212> PRT
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<220>
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<400> 1000

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

Gly Lys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1001
<211> 36
<212> PRT
<213> Artificial sequence

<220>
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<400> 1001

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

Gly Cys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1002
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1002

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

Gly Asn Gly Ser Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1003
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1003

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

Gly Cys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1004
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1004

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1005
<211> 32
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1005

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

Asn Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25 30

<210> 1006
<211> 32
<212> PRT
<213> Artificial sequence

<220>
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<400> 1006

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

Asn Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
20 25 30

<210> 1007
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1007

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1008
<211> 34
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1008

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

Gly Pro Asn Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Ala
20 25 30

Arg Ala

<210> 1009
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1009

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1010
<211> 36
<212> PRT
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<400> 1010

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1011
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1011

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Cys Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1012
<211> 36
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1012

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

Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Ala Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1013
<211> 36
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1013

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

Gly Lys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

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<400> 1014

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

Gly Cys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1015
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<212> PRT
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<400> 1015

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

Gly Asn Gly Ser Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1016
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<400> 1016

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

Gly Cys Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
20 25 30

Ala Ala Arg Ala
35

<210> 1017
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<400> 1017

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

Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr
20 25 30

Leu Arg Gln Trp Leu Ala Ala Arg Ala
35 40

<210> 1018
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<400> 1018

Gly Gly Gly Lys Gly Gly Gly Gly
1 5

<210> 1019
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<400> 1019

Gly Gly Gly Asn Gly Ser Gly Gly
1 5

<210> 1020
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<400> 1020

Gly Gly Gly Cys Gly Gly Gly Gly
1 5

<210> 1021
<211> 5
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<220>
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<400> 1021

Gly Pro Asn Gly Gly
1 5

<210> 1022
<211> 29
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<210> 1023
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<400> 1023
ctagttattg ctcagcgg 18

<210> 1024
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<400> 1024
ccgggtaaag gtggaggtgg tggtatcga 29

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<400> 1025
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<210> 1026
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cgtacaggtt tacgcaagaa aatgg 25

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<400> 1027
ccacctccac ctttacccgg agagtgggag 30

<210> 1028
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<400> 1028
cgtacaggtt tacgcaagaa aatgg 25

<210> 1029
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<400> 1029
ctagttattg ctcagcgg 18

<210> 1030
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cgtacaggtt tacgcaagaa aatgg 25

<210> 1031
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<400> 1031
ctagttattg ctcagcgg 18

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<220>
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taagccatgc atttgtacag tcccagaagt atcatctgtc ttcatcttcc ccccaaagcc 120

caaggatgtg ctcaccatta ctctgactcc taaggtcacg tgtgttgtgg tagacatcag 180

caaggatgat cccgaggtcc agttcagctg gtttgtagat gatgtggagg tgcacacagc 240

tcagacgcaa ccccgggagg agcagttcaa cagcactttc cgctcagtca gtgaacttcc 300

catcatgcac caggactggc tcaatggcaa ggagttcaaa tgcagggtca acagtgcagc 360

tttccctgcc cccatcgaga aaaccatctc caaaaccaaa ggcagaccga aggctccaca 420

ggtgtacacc attccacctc ccaaggagca gatggccaag gataaagtca gtctgacctg 480

catgataaca gacttcttcc ctgaagacat tactgtggag tggcagtgga atgggcagcc 540

agcggagaac tacaagaaca ctcagcccat catggacaca gatggctctt acttcgtcta 600

cagcaagctc aatgtgcaga agagcaactg ggaggcagga aatactttca cctgctctgt 660

gttacatgag ggcctgcaca accaccatac tgagaagagc ctctcccact ctccgggtaa 720

aggtggaggt ggtggtatcg aaggtccgac tctgcgtcag tggctggctg ctcgtgctgg 780

tggtggaggt ggcggcggag gtattgaggg cccaaccctt cgccaatggc ttgcagcacg 840

cgcataatct cgaggatccg cggaaagaag aagaagaaga agaaagcccg aaagg 895

<210> 1033
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<212> PRT
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<220>
<223> Synthetic peptide

<400> 1033

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Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr
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Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp
        35                  40                  45

Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
    50                  55                  60

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

Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
                85                  90                  95

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
            100                 105                 110

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

Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
    130                 135                 140

Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
145                 150                 155                 160

Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
                165                 170                 175

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

Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
        195                 200                 205

Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
    210                 215                 220

Lys Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
225                 230                 235                 240

Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro
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Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
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caaggatgat cccgaggtcc agttcagctg gtttgtagat gatgtggagg tgcacacagc 240

tcagacgcaa ccccgggagg agcagttcaa cagcactttc cgctcagtca gtgaacttcc 300

catcatgcac caggactggc tcaatggcaa ggagttcaaa tgcagggtca acagtgcagc 360

tttccctgcc cccatcgaga aaaccatctc caaaaccaaa ggcagaccga aggctccaca 420

ggtgtacacc attccacctc ccaaggagca gatggccaag gataaagtca gtctgacctg 480

catgataaca gacttcttcc ctgaagacat tactgtggag tggcagtgga atgggcagcc 540

agcggagaac tacaagaaca ctcagcccat catggacaca gatggctctt acttcgtcta 600

cagcaagctc aatgtgcaga agagcaactg ggaggcagga aatactttca cctgctctgt 660

gttacatgag ggcctgcaca accaccatac tgagaagagc ctctcccact ctccgggtaa 720

aggtggaggt ggtggtatcg aaggtccgac tctgcgtcag tggctggctg ctcgtgctgg 780

tggtggaggt ggcggcggag gtattgaggg cccaaccctt cgccaatggc ttgcagcacg 840

cgcataatct cgaggatccg cggaaagaag aagaagaaga agaaagcccg aaagg 895

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<211> 266
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<220>
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<400> 1035

Met Val Asp Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser
1 5 10 15

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

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

Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr
50 55 60

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

Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu
85 90 95

Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys
100 105 110

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

Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr
130 135 140

Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln
145 150 155 160

Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met
165 170 175

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

Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
195 200 205

Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
210 215 220

Lys Gly Gly Gly Gly Gly Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu
225 230 235 240

Ala Ala Arg Ala Gly Gly Gly Gly Gly Gly Gly Gly Ile Glu Gly Pro
245 250 255

Thr Leu Arg Gln Trp Leu Ala Ala Arg Ala
260 265

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<400> 1036

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1 5 10

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<400> 1037

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

<210> 1038
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<400> 1038

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1 5 10

<210> 1039
<211> 14
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<400> 1039

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

<210> 1040
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Trp Tyr Pro Cys Tyr Glu Phe His Phe Trp Cys Tyr Asp Leu
1 5 10

<210> 1041
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<400> 1041

Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu
1 5 10

<210> 1042
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<212> PRT
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<400> 1042

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

<210> 1043
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<220>
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<400> 1043

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

<210> 1044
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<400> 1044

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

<210> 1045
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<400> 1045

His Lys Phe Cys Pro Trp Trp Ala Leu Phe Cys Trp Asp Phe
1 5 10

<210> 1046
<211> 14
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<400> 1046

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

<210> 1047
<211> 14
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<400> 1047

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

<210> 1048
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<400> 1048

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

<210> 1049
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<220>
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<400> 1049

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

<210> 1050
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<400> 1050

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

<210> 1051
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<400> 1051

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

<210> 1052
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<220>
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<400> 1052

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

<210> 1053
<211> 14
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<220>
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<400> 1053

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

<210> 1054
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<220>
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<400> 1054

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

<210> 1055
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1055

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

<210> 1056
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1056

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

<210> 1057
<211> 14
<212> PRT
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<220>
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<400> 1057

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

<210> 1058
<211> 14
<212> PRT
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<220>
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<400> 1058

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

<210> 1059
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1059

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

<210> 1060
<211> 14
<212> PRT
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<220>
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<400> 1060

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

<210> 1061
<211> 14
<212> PRT
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<220>
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<400> 1061

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

<210> 1062
<211> 14
<212> PRT
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<220>
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<400> 1062

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

<210> 1063
<211> 14
<212> PRT
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<220>
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<400> 1063

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

<210> 1064
<211> 14
<212> PRT
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<220>
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<400> 1064

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

<210> 1065
<211> 14
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<220>
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<400> 1065

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

<210> 1066
<211> 14
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<400> 1066

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

<210> 1067
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<400> 1067

Gly Val Arg Cys Pro Lys Gly His Leu Trp Cys Leu Tyr Pro
1 5 10

<210> 1068
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<220>
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<400> 1068

His Trp Ala Cys Gly Tyr Trp Pro Trp Ser Cys Lys Trp Val
1 5 10

<210> 1069
<211> 14
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<220>
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<400> 1069

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

<210> 1070
<211> 14
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<220>
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<400> 1070

Thr Thr Trp Cys Ile Ser Pro Met Trp Phe Cys Ser Gln Gln
1 5 10

<210> 1071
<211> 14
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<220>
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<400> 1071

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

<210> 1072
<211> 14
<212> PRT
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<220>
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<400> 1072

Pro Asp Trp Cys Val Ser Pro Arg Trp Tyr Cys Asn Met Trp
1 5 10

<210> 1073
<211> 14
<212> PRT
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<220>
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<400> 1073

Val Trp Lys Cys His Trp Phe Gly Met Asp Cys Glu Pro Thr
1 5 10

<210> 1074
<211> 14
<212> PRT
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<220>
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<400> 1074

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

<210> 1075
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1075

Trp Phe Gln Cys Gly Ser Thr Leu Phe Trp Cys Tyr Asn Leu
1 5 10

<210> 1076
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<212> PRT
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<220>
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<400> 1076

Trp Ser Pro Cys Tyr Asp His Tyr Phe Tyr Cys Tyr Thr Ile
1 5 10

<210> 1077
<211> 14
<212> PRT
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<220>
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<400> 1077

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

<210> 1078
<211> 14
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<400> 1078

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

<210> 1079
<211> 14
<212> PRT
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<220>
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<400> 1079

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

<210> 1080
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1080

Val Val Gly Cys Lys Trp Tyr Glu Ala Trp Cys Tyr Asn Lys
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<210> 1081
<211> 14
<212> PRT
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<220>
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<400> 1081

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

<210> 1082
<211> 14
<212> PRT
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<220>
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<400> 1082

Asp Ser Asn Cys Pro Trp Tyr Phe Leu Ser Cys Val Ile Phe
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<210> 1083
<211> 14
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<220>
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<400> 1083

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

<210> 1084
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<220>
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<400> 1084

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

<210> 1085
<211> 14
<212> PRT
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<220>
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<400> 1085

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

<210> 1086
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<220>
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<400> 1086

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

<210> 1087
<211> 14
<212> PRT
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<220>
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<400> 1087

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

<210> 1088
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<400> 1088

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

<210> 1089
<211> 14
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<220>
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<400> 1089

Phe Trp Arg Cys Ala Ile Gly Ile Asp Lys Cys Lys Arg Val
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<210> 1090
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1090

Asn Leu Gly Cys Lys Trp Tyr Glu Val Trp Cys Phe Thr Tyr
1 5 10

<210> 1091
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1091

Ile Asp Leu Cys Asn Met Trp Asp Gly Met Cys Tyr Pro Pro
1 5 10

<210> 1092
<211> 14
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1092

Glu Met Pro Cys Asn Ile Trp Gly Trp Met Cys Pro Pro Val
1 5 10

<210> 1093
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1093

Trp Phe Arg Cys Val Leu Thr Gly Ile Val Asp Trp Ser Glu Cys Phe
1 5 10 15

Gly Leu

<210> 1094
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1094

Gly Phe Ser Cys Thr Phe Gly Leu Asp Glu Phe Tyr Val Asp Cys Ser
1 5 10 15

Pro Phe

<210> 1095
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1095

Leu Pro Trp Cys His Asp Gln Val Asn Ala Asp Trp Gly Phe Cys Met
1 5 10 15

Leu Trp

<210> 1096
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1096

Tyr Pro Thr Cys Ser Glu Lys Phe Trp Ile Tyr Gly Gln Thr Cys Val
1 5 10 15

Leu Trp

<210> 1097
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1097

Leu Gly Pro Cys Pro Ile His His Gly Pro Trp Pro Gln Tyr Cys Val
1 5 10 15

Tyr Trp

<210> 1098
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1098

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

Ser Phe

<210> 1099
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1099

His Trp Gly Cys Glu Asp Leu Met Trp Ser Trp His Pro Leu Cys Arg
1 5 10 15

Arg Pro

<210> 1100
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1100

Leu Pro Leu Cys Asp Ala Asp Met Met Pro Thr Ile Gly Phe Cys Val
1 5 10 15

Ala Tyr

<210> 1101
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1101

Ser His Trp Cys Glu Thr Thr Phe Trp Met Asn Tyr Ala Lys Cys Val
1 5 10 15

His Ala

<210> 1102
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1102

Leu Pro Lys Cys Thr His Val Pro Phe Asp Gln Gly Gly Phe Cys Leu
1 5 10 15

Trp Tyr

<210> 1103
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1103

Phe Ser Ser Cys Trp Ser Pro Val Ser Arg Gln Asp Met Phe Cys Val
1 5 10 15

Phe Tyr

<210> 1104
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1104

Ser His Lys Cys Glu Tyr Ser Gly Trp Leu Gln Pro Leu Cys Tyr Arg
1 5 10 15

Pro

<210> 1105
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1105

Pro Trp Trp Cys Gln Asp Asn Tyr Val Gln His Met Leu His Cys Asp
1 5 10 15

Ser Pro

<210> 1106
<211> 18
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1106

Trp Phe Arg Cys Met Leu Met Asn Ser Phe Asp Ala Phe Gln Cys Val
1 5 10 15

Ser Tyr

<210> 1107
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1107

Pro Asp Ala Cys Arg Asp Gln Pro Trp Tyr Met Phe Met Gly Cys Met
1 5 10 15

Leu Gly

<210> 1108
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1108

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

<210> 1109
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1109

Ser Ala Tyr Cys Ile Ile Thr Glu Ser Asp Pro Tyr Val Leu Cys Val
1 5 10 15

Pro Leu

<210> 1110
<211> 18
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1110

Pro Ser Ile Cys Glu Ser Tyr Ser Thr Met Trp Leu Pro Met Cys Gln
1 5 10 15

His Asn

<210> 1111
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1111

Trp Leu Asp Cys His Asp Asp Ser Trp Ala Trp Thr Lys Met Cys Arg
1 5 10 15

Ser His

<210> 1112
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1112

Tyr Leu Asn Cys Val Met Met Asn Thr Ser Pro Phe Val Glu Cys Val
1 5 10 15

Phe Asn

<210> 1113
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1113

Tyr Pro Trp Cys Asp Gly Phe Met Ile Gln Gln Gly Ile Thr Cys Met
1 5 10 15

Phe Tyr

<210> 1114
<211> 18

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1114

Phe Asp Tyr Cys Thr Trp Leu Asn Gly Phe Lys Asp Trp Lys Cys Trp
1 5 10 15

Ser Arg

<210> 1115
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1115

Leu Pro Leu Cys Asn Leu Lys Glu Ile Ser His Val Gln Ala Cys Val
1 5 10 15

Leu Phe

<210> 1116
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1116

Ser Pro Glu Cys Ala Phe Ala Arg Trp Leu Gly Ile Glu Gln Cys Gln
1 5 10 15

Arg Asp

<210> 1117
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1117

Tyr Pro Gln Cys Phe Asn Leu His Leu Leu Glu Trp Thr Glu Cys Asp
1 5 10 15

Trp Phe

<210> 1118
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1118

Arg Trp Arg Cys Glu Ile Tyr Asp Ser Glu Phe Leu Pro Lys Cys Trp
1 5 10 15

Phe Phe

<210> 1119
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1119

Leu Val Gly Cys Asp Asn Val Trp His Arg Cys Lys Leu Phe
1 5 10

<210> 1120
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1120

Ala Gly Trp Cys His Val Trp Gly Glu Met Phe Gly Met Gly Cys Ser
1 5 10 15

Ala Leu

<210> 1121
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1121

His His Glu Cys Glu Trp Met Ala Arg Trp Met Ser Leu Asp Cys Val
1 5 10 15

Gly Leu

<210> 1122
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1122

Phe Pro Met Cys Gly Ile Ala Gly Met Lys Asp Phe Asp Phe Cys Val
1 5 10 15

Trp Tyr

<210> 1123
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1123

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

Arg Pro

<210> 1124
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1124

Tyr Asn Phe Cys Ser Tyr Leu Phe Gly Val Ser Lys Glu Ala Cys Gln
1 5 10 15

Leu Pro

<210> 1125
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1125

Ala His Trp Cys Glu Gln Gly Pro Trp Arg Tyr Gly Asn Ile Cys Met
1 5 10 15

Ala Tyr

<210> 1126
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1126

Asn Leu Val Cys Gly Lys Ile Ser Ala Trp Gly Asp Glu Ala Cys Ala
1 5 10 15

Arg Ala

<210> 1127
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1127

His Asn Val Cys Thr Ile Met Gly Pro Ser Met Lys Trp Phe Cys Trp
1 5 10 15

Asn Asp

<210> 1128
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1128

Asn Asp Leu Cys Ala Met Trp Gly Trp Arg Asn Thr Ile Trp Cys Gln
1 5 10 15

Asn Ser

<210> 1129
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1129

Pro Pro Phe Cys Gln Asn Asp Asn Asp Met Leu Gln Ser Leu Cys Lys
1 5 10 15

Leu Leu

<210> 1130
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1130

Trp Tyr Asp Cys Asn Val Pro Asn Glu Leu Leu Ser Gly Leu Cys Arg
1 5 10 15

Leu Phe

<210> 1131
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1131

Tyr Gly Asp Cys Asp Gln Asn His Trp Met Trp Pro Phe Thr Cys Leu
1 5 10 15

Ser Leu

<210> 1132
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1132

Gly Trp Met Cys His Phe Asp Leu His Asp Trp Gly Ala Thr Cys Gln
1 5 10 15

Pro Asp

<210> 1133
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1133

Tyr Phe His Cys Met Phe Gly Gly His Glu Phe Glu Val His Cys Glu
1 5 10 15

Ser Phe

<210> 1134
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1134

Ala Tyr Trp Cys Trp His Gly Gln Cys Val Arg Phe
1 5 10

<210> 1135
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1135

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

Arg Pro Phe

<210> 1136
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1136

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> 1137
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1137

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

Lys Phe Thr

<210> 1138
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1138

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> 1139
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1139

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> 1140
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1140

Lys Arg Leu Leu Glu Gln Phe Met Asn Asp Leu Ala Glu Leu Val Ser
1 5 10 15

Gly His Ser

<210> 1141
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1141

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> 1142
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1142

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> 1143
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1143

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> 1144
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1144

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> 1145
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1145

Met Leu Ser Glu Phe Glu Glu Phe Leu Gly Asn Leu Val His Arg Gln
1 5 10 15

Glu Ala

<210> 1146
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1146

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> 1147
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1147

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> 1148
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1148

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> 1149
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1149

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> 1150
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1150

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> 1151
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1151

Arg Ala Thr Leu Leu Lys Asp Phe Trp Gln Leu Val Glu Gly Tyr Gly
1 5 10 15

Asp Asn

<210> 1152
<211> 16
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1152

Glu Glu Leu Leu Arg Glu Phe Tyr Arg Phe Val Ser Ala Phe Asp Tyr
1 5 10 15

<210> 1153
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1153

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> 1154
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1154

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> 1155
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1155

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> 1156
<211> 20
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1156

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> 1157
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1157

Gln Phe Pro Phe Tyr Val Phe Asp Asp Leu Pro Ala Gln Leu Glu Tyr
1 5 10 15

Trp Ile Ala

<210> 1158
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1158

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> 1159
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1159

Glu Ala Leu Phe Gln Asn Phe Phe Arg Asp Val Leu Thr Leu Ser Glu
1 5 10 15

Arg Glu Tyr

<210> 1160
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1160

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> 1161
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1161

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> 1162
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1162

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> 1163
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1163

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> 1164
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1164

Ile Leu Leu Leu Asp Glu Tyr Lys Lys Asp Trp Lys Ser Trp Phe
1 5 10 15

<210> 1165
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1165

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> 1166
<211> 43
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1166

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> 1167
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1167

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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
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<210> 1168
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1168

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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
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<210> 1169
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1169

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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
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Val Met
50

<210> 1170
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1170

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> 1171
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1171

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> 1172
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1172

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> 1173
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1173

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> 1174
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1174

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> 1175
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1175

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> 1176
<211> 34
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1176

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> 1177
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1177

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> 1178
<211> 20
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1178

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> 1179
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1179

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> 1180
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1180

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> 1181
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1181

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> 1182
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1182

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> 1183
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1183

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> 1184
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1184

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> 1185
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1185

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> 1186
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1186

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> 1187
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1187

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> 1188
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1188

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> 1189
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1189

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> 1190
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1190

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> 1191
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1191

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> 1192
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1192

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> 1193
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1193

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> 1194
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1194

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> 1195
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1195

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> 1196
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1196

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> 1197
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1197

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> 1198
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1198

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> 1199
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1199

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> 1200
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1200

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> 1201
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1201

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> 1202
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1202

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> 1203
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1203

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> 1204
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1204

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> 1205
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1205

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> 1206
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1206

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> 1207
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1207

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> 1208
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1208

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> 1209
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1209

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> 1210
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1210

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> 1211
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1211

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> 1212
<211> 20
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1212

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> 1213
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1213

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> 1214
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1214

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> 1215
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1215

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> 1216
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1216

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> 1217
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1217

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> 1218
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1218

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> 1219
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1219

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> 1220
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1220

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> 1221
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1221

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> 1222
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1222

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> 1223
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1223

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> 1224
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1224

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> 1225
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1225

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> 1226
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1226

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> 1227
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1227

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> 1228
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1228

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> 1229
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1229

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> 1230
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1230

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> 1231
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1231

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> 1232
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1232

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> 1233
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1233

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> 1234
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1234

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> 1235
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1235

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> 1236
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1236

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> 1237
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1237

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> 1238
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1238

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> 1239
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1239

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> 1240
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1240

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> 1241
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1241

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> 1242
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1242

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> 1243
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1243

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> 1244
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1244

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> 1245
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1245

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> 1246
<211> 22
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1246

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> 1247
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1247

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> 1248
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1248

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> 1249
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1249

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> 1250
<211> 22

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1250

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> 1251
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1251

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> 1252
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1252

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> 1253
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1253

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> 1254
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1254

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> 1255
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1255

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> 1256
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1256

Asp Glu Asp Ser Leu Gln Gln Leu Leu Met Trp Leu Asp Gln Lys Leu
1 5 10 15

Ala Ser Gly Pro Gln Leu
20

<210> 1257
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1257

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> 1258
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1258

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> 1259
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1259

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> 1260
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1260

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> 1261
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1261

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> 1262
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1262

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> 1263
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1263

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> 1264
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1264

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> 1265
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1265

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> 1266
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1266

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> 1267
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1267

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> 1268
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1268

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> 1269
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1269

Gly Val Glu Ser Leu Gln Gln Leu Leu Ile Phe Leu Asp His Met Leu
1 5 10 15

Val Ser Gly Pro His Asp
20

<210> 1270
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1270

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> 1271
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1271

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> 1272
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1272

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> 1273
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1273

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> 1274
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1274

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
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<210> 1275
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1275

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> 1276
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1276

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> 1277
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1277

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> 1278
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1278

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> 1279
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1279

Arg Ala Thr Leu Leu Lys Asp Phe Trp Gln Leu Val Glu Gly Tyr Gly
1 5 10 15

Asp Asn

<210> 1280
<211> 22
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1280

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> 1281
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1281

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> 1282
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1282

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> 1283
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1283

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> 1284
<211> 22

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1284

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> 1285
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1285

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> 1286
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1286

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> 1287
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1287

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> 1288
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1288

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> 1289
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1289

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> 1290
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1290

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> 1291
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1291

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> 1292
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1292

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> 1293
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1293

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> 1294
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1294

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> 1295
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1295

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> 1296
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1296

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> 1297
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1297

Ser Thr Arg Ala Thr Leu Leu Asn Asp Leu Trp Gln Leu Met Lys Gly
1 5 10 15

Trp Ala Glu Asp Arg Gly
20

<210> 1298
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1298

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

Trp Gly Asp Asn Phe Gly
20

<210> 1299
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1299

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> 1300
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1300

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> 1301
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1301

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> 1302
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1302

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> 1303
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1303

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> 1304
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1304

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> 1305
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1305

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> 1306
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1306

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> 1307
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1307

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> 1308
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1308

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> 1309
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1309

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> 1310
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1310

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> 1311
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1311

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> 1312
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1312

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> 1313
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1313

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> 1314
<211> 22
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1314

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> 1315
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1315

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> 1316
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1316

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> 1317
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1317

Trp Tyr Arg Asp Met Ser Met Leu Glu Gly Leu Leu Glu Val Leu Asp
1 5 10 15

Arg Leu Gly Gln Gln Arg
20

<210> 1318
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1318

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> 1319
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1319

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> 1320
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1320

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> 1321
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1321

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> 1322
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1322

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> 1323
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1323

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> 1324
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1324

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> 1325
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1325

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> 1326
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1326

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> 1327
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1327

Phe Asp Phe Leu Gln Trp Leu Gln Asn His Arg Ser Glu Val Glu His
1 5 10 15

Trp Leu Val Met Asp Val
20

<210> 1328
<211> 56
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1328

Met Gly Ala Gln Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr
1 5 10 15

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

Ser Gly Ser Gly Ser Ala Thr Gly Trp Tyr Pro Cys Tyr Glu Gly His
35 40 45

Phe Trp Cys Tyr Asp Leu Leu Glu
50 55

<210> 1329
<211> 54
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1329

Ala Gln Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp Cys Tyr Asp Leu
1 5 10 15

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
20 25 30

Ser Gly Ser Ala Thr Gly Trp Tyr Pro Cys Tyr Glu Gly His Phe Trp
35 40 45

Cys Tyr Asp Leu Leu Glu
50

<210> 1330
<211> 56
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1330

Met Gly Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp Val Gln Cys Tyr
1 5 10 15

Gln Phe Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser
20 25 30

Ser Gly Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys Lys Trp Trp Asp
35 40 45

Val Gln Cys Tyr Gln Phe Leu Glu
50 55

<210> 1331
<211> 54
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1331

Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp Val Gln Cys Tyr Gln Phe
1 5 10 15

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
20 25 30

Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys Lys Trp Trp Asp Val Gln
35 40 45

Cys Tyr Gln Phe Leu Glu
50

<210> 1332
<211> 56
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1332

Met Gly Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp Val Asp Cys Tyr
1 5 10 15

Gln Phe Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser
20 25 30

Ser Gly Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys Lys Trp Trp Asp
35 40 45

Val Asp Cys Tyr Gln Phe Leu Glu
50 55

<210> 1333
<211> 54
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1333

Ala Gln Ile Phe Gly Cys Lys Trp Trp Asp Val Asp Cys Tyr Gln Phe
1 5 10 15

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
20 25 30

Ser Gly Ser Ala Thr Gly Ile Phe Gly Cys Lys Trp Trp Asp Val Asp
35 40 45

Cys Tyr Gln Phe Leu Glu
50

<210> 1334
<211> 68
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1334

Ala Gln Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys
1 5 10 15

Pro Pro Glu Gly Trp Glu Leu Glu Gly Ser Gly Ser Ala Thr Gly Gly
20 25 30

Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Leu Ala
35 40 45

Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro Glu Gly
50 55 60

Trp Glu Leu Glu
65

<210> 1335
<211> 64
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1335

Ala Gln Leu Ala Asp His Gly Gln Cys Ile Arg Trp Pro Trp Met Cys
1 5 10 15

Pro Pro Glu Gly Trp Glu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
20 25 30

Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Leu Ala Asp His
35 40 45

Gly Gln Cys Ile Arg Trp Pro Trp Met Cys Pro Pro Glu Gly Trp Glu
50 55 60

<210> 1336
<211> 68
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1336

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

Pro Pro Gln Gly Trp Lys Leu Glu Gly Ser Gly Ser Ala Thr Gly Gly
20 25 30

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Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Ser Glu
        35                  40                  45

Tyr Gln Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Gln Gly
    50                  55                  60

Trp Lys Leu Glu
65
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<210> 1337
<211> 64
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1337

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

Pro Pro Gln Gly Trp Lys Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
            20                  25                  30

Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Ser Glu Tyr Gln
        35                  40                  45

Gly Leu Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Lys
    50                  55                  60
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<210> 1338
<211> 67
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1338

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

Pro Pro Gln Gly Trp Gly Leu Glu Gly Ser Gly Ser Ala Thr Gly Gly
            20                  25                  30

Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Thr Phe
        35                  40                  45

Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Gln Gly
    50                  55                  60

Trp Gly Leu
65
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<210> 1339
<211> 68
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1339

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

Pro Pro Gln Gly Trp Gly Leu Glu Gly Ser Gly Ser Ala Thr Gly Gly
20 25 30

Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Val Ala
35 40 45

Asp His Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Gln Gly
50 55 60

Trp Gly Leu Glu
65

<210> 1340
<211> 64
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1340

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

Pro Pro Gln Gly Trp Gly Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
20 25 30

Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Val Ala Asp His
35 40 45

Gly His Cys Thr Arg Trp Pro Trp Val Cys Pro Pro Gln Gly Trp Gly
50 55 60

<210> 1341
<211> 68
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1341

Ala Gln Pro Glu Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys
1 5 10 15

Pro Pro Gln Gly Trp Gly Leu Glu Gly Ser Gly Ser Ala Thr Gly Gly
            20   25   30

Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Pro Glu
        35   40   45

Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Gln Gly
    50   55   60

Trp Gly Leu Glu
65

<210> 1342
<211> 64
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1342

Ala Gln Pro Glu Ser Gln Gly His Cys Thr Arg Trp Pro Trp Met Cys
1   5   10   15

Pro Pro Gln Gly Trp Gly Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly
            20   25   30

Gly Gly Ala Ser Ser Gly Ser Gly Ser Ala Thr Gly Pro Glu Ser Gln
        35   40   45

Gly His Cys Thr Arg Trp Pro Trp Met Cys Pro Pro Gln Gly Trp Gly
    50   55   60

<210> 1343

<400> 1343
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<210> 1344
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1344

Cys Leu Cys Arg Gly Asp Cys Ile Cys
1   5

<210> 1345
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1345

Cys Trp Asp Asp Gly Trp Leu Cys
1 5

<210> 1346
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1346

Cys Trp Asp Asp Leu Trp Trp Leu Cys
1 5

<210> 1347
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1347

Cys Trp Asp Asp Gly Leu Met Cys
1 5

<210> 1348
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1348

Cys Trp Asp Asp Gly Trp Met Cys
1 5

<210> 1349
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1349

Cys Ser Trp Asp Asp Gly Trp Leu Cys
1 5

<210> 1350
<211> 9
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1350

Cys Pro Asp Asp Leu Trp Trp Leu Cys
1 5

<210> 1351
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1351

Asn Gly Arg
1

<210> 1352
<211> 3
<212> PRT
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<220>
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<400> 1352

Gly Ser Leu
1

<210> 1353
<211> 3
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1353

Arg Gly Asp
1

<210> 1354
<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1354

Cys Gly Arg Glu Cys Pro Arg Leu Cys Gln Ser Ser Cys
1 5 10

<210> 1355

<211> 13
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1355

Cys Asn Gly Arg Cys Val Ser Gly Cys Ala Gly Arg Cys
1 5 10

<210> 1356
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1356

Cys Leu Ser Gly Ser Leu Ser Cys
1 5

<210> 1357
<211> 3
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1357

Gly Ser Leu
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<220>
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<400> 1358

Asn Gly Arg Ala His Ala
1 5

<210> 1359
<211> 5
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<220>
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<400> 1359

Cys Asn Gly Arg Cys
1 5

<210> 1360
<211> 9
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<220>
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<400> 1360

Cys Asp Cys Arg Gly Asp Cys Phe Cys
1 5

<210> 1361
<211> 7
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<220>
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<400> 1361

Cys Gly Ser Leu Val Arg Cys
1 5

<210> 1362
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<400> 1362

Asp Leu Xaa Xaa Leu
1 5

<210> 1363
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<400> 1363

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr Thr Leu
1 5 10

<210> 1364
<211> 10
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<220>
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<400> 1364

Arg Thr Asp Leu Asp Ser Leu Arg Thr Tyr
1 5 10

<210> 1365
<211> 9
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<220>
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<400> 1365

Arg Thr Asp Leu Asp Ser Leu Arg Thr
1 5

<210> 1366
<211> 8
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<220>
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<400> 1366

Arg Thr Asp Leu Asp Ser Leu Arg
1 5

<210> 1367
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 1367

Gly Asp Leu Asp Leu Leu Lys Leu Arg Leu Thr Leu
1 5 10

<210> 1368
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 1368

Gly Asp Leu His Ser Leu Arg Gln Leu Leu Ser Arg
1 5 10

<210> 1369
<211> 12
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<220>
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<400> 1369

Arg Asp Asp Leu His Met Leu Arg Leu Gln Leu Trp
1 5 10

<210> 1370
<211> 12
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<220>
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<400> 1370

Ser Ser Asp Leu His Ala Leu Lys Lys Arg Tyr Gly
1 5 10

<210> 1371
<211> 12
<212> PRT
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<220>
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<400> 1371

Arg Gly Asp Leu Lys Gln Leu Ser Glu Leu Thr Trp
1 5 10

<210> 1372
<211> 7
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<220>
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<220>
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<223> Xaa=any amino acid

<400> 1372

Cys Xaa Xaa Arg Gly Asp Cys
1 5

<210> 1373
<211> 27
<212> PRT
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<220>
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<400> 1373

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1               5                   10                  15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
            20                  25
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<210> 1374
<211> 27
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<220>
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<400> 1374

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1               5                   10                  15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
            20                  25
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<210> 1375
<211> 30
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1375

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1               5                   10                  15

Met Lys Glu Ala Ser Asn Val Phe Pro Ser Arg Arg Ser Arg
            20                  25                  30
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<210> 1376
<211> 30
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<220>
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<400> 1376

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1               5                   10                  15

Ala Met Leu Gly Leu Leu Ser Thr Ile His Ser Ser Ser Arg
            20                  25                  30
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<210> 1377
<211> 31
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<220>
<223> Synthetic peptide

<400> 1377

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

Ala Thr Arg Ile Gln Asp Leu Leu Ile Ala Ser Arg Pro Ser Arg
20 25 30

<210> 1378
<211> 31
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1378

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

Asp Ala Thr Arg Thr Ser Ile Pro Pro Ser Leu Gln Asn Ser Arg
20 25 30

<210> 1379
<211> 18
<212> PRT
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<220>
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<400> 1379

Asp Val Tyr Thr Lys Lys Glu Leu Ile Glu Cys Ala Arg Arg Val Ser
1 5 10 15

Glu Lys

<210> 1380
<211> 5
<212> PRT
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Cys Arg Gly Asp Gly Xaa Cys
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<220>
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<400> 1382

Cys Ala Arg Arg Leu Asp Ala Pro Cys
1 5

<210> 1383
<211> 9
<212> PRT
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<220>
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<400> 1383

Cys Pro Ser Arg Leu Asp Ser Pro Cys
1 5

<210> 1384
<211> 9
<212> PRT
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<220>
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<400> 1384

Cys Asp Cys Arg Gly Asp Cys Phe Cys
1 5

<210> 1385
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<220>
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<400> 1385

Cys Asp Cys Arg Gly Asp Cys Leu Cys
1 5

<210> 1386
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<220>
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<400> 1386

Arg Gly Asp Leu Ala Ala Leu Ser Ala Pro Pro Val
1 5 10

<210> 1387
<211> 12
<212> PRT
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<220>
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<400> 1387

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 1388
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<212> PRT
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<220>
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<400> 1388

Asp Ile Thr Trp Asp Glu Leu Trp Lys Ile Met Asn
1 5 10

<210> 1389
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<212> PRT
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<220>
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<400> 1389

Asp Tyr Thr Trp Phe Glu Leu Trp Asp Met Met Gln
1 5 10

<210> 1390
<211> 12
<212> PRT

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<220>
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<400> 1390

Gln Ile Thr Trp Ala Gln Leu Trp Asn Met Met Lys
1 5 10

<210> 1391
<211> 12
<212> PRT
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<220>
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<400> 1391

Asp Met Thr Trp His Asp Leu Trp Thr Leu Met Ser
1 5 10

<210> 1392
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 1392

Asp Tyr Ser Trp His Asp Leu Trp Glu Met Met Ser
1 5 10

<210> 1393
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 1393

Glu Ile Thr Trp Asp Gln Leu Trp Glu Val Met Asn
1 5 10

<210> 1394
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<212> PRT
<213> Artificial sequence

<220>
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<400> 1394

His Val Ser Trp Glu Gln Leu Trp Asp Ile Met Asn
1 5 10

<210> 1395

<211> 12
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<400> 1395

His Ile Thr Trp Asp Gln Leu Trp Arg Ile Met Thr
1 5 10

<210> 1396
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<400> 1396

Arg Asn Met Ser Trp Leu Glu Leu Trp Glu His Met Lys
1 5 10

<210> 1397
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<212> PRT
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<220>
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<400> 1397

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

Ser Gln

<210> 1398
<211> 14
<212> PRT
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<220>
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<400> 1398

His Arg Ala Glu Trp Leu Ala Leu Trp Glu Gln Met Ser Pro
1 5 10

<210> 1399
<211> 14
<212> PRT
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<400> 1399

Lys Lys Glu Asp Trp Leu Ala Leu Trp Arg Ile Met Ser Val
1 5 10

<210> 1400
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<212> PRT
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<400> 1400

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1 5 10

<210> 1401
<211> 12
<212> PRT
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<400> 1401

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 1402
<211> 12
<212> PRT
<213> Artificial sequence

<220>
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<400> 1402

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 1403
<211> 12
<212> PRT
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<220>
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<400> 1403

Asp Ile Thr Trp Asp Gln Leu Trp Asp Leu Met Lys
1 5 10

<210> 1404
<211> 16
<212> PRT
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<220>
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<400> 1404

Cys Gln Asn Arg Tyr Thr Asp Leu Val Ala Ile Gln Asn Lys Asn Glu
1 5 10 15

<210> 1405
<211> 17
<212> PRT
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<220>
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<400> 1405

Ala Glu Asn Trp Ala Asp Asn Glu Pro Asn Asn Lys Arg Asn Asn Glu
1 5 10 15

Asp

<210> 1406
<211> 19
<212> PRT
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<220>
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<400> 1406

Arg Lys Asn Asn Lys Thr Trp Thr Trp Val Gly Thr Lys Lys Ala Leu
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Thr Asn Glu

<210> 1407
<211> 13
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<220>
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<400> 1407

Lys Lys Ala Leu Thr Asn Glu Ala Glu Asn Trp Ala Asp
1 5 10

<210> 1408
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<400> 1408

Cys Gln Xaa Arg Tyr Thr Asp Leu Val Ala Ile Gln Asn Lys Xaa Glu
1 5 10 15

<210> 1409
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<400> 1409

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Asp

<210> 1410
<211> 30
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1410

Ser Ser Gln Asn Trp Asp Met Glu Ala Gly Val Glu Asp Leu Thr Ala
1 5 10 15

Ala Met Leu Gly Leu Leu Ser Thr Ile His Ser Ser Ser Arg
20 25 30

<210> 1411
<211> 31
<212> PRT
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<220>
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<400> 1411

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

Ala Thr Arg Ile Gln Asp Leu Leu Ile Ala Ser Arg Pro Ser Arg
20 25 30

<210> 1412
<211> 31
<212> PRT
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<220>
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<400> 1412

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

Asp Ala Thr Arg Thr Ser Ile Pro Pro Ser Leu Gln Asn Ser Arg
20 25 30

<210> 1413
<211> 18
<212> PRT
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<220>
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<400> 1413

Asp Val Tyr Thr Lys Lys Glu Leu Ile Glu Cys Ala Arg Arg Val Ser
1 5 10 15

Glu Lys

<210> 1414
<211> 27
<212> PRT
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<220>
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<400> 1414

Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Gly Val Ser
1 5 10 15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
20 25

<210> 1415
<211> 27
<212> PRT

<213> Artificial sequence

<220>
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<400> 1415

Ser Thr Gly Gly Phe Asp Asp Val Tyr Asp Trp Ala Arg Arg Val Ser
1 5 10 15

Ser Ala Leu Thr Thr Thr Leu Val Ala Thr Arg
20 25

<210> 1416
<211> 30
<212> PRT
<213> Artificial sequence

<220>
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<400> 1416

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

Met Lys Glu Ala Ser Asn Val Phe Pro Ser Arg Arg Ser Arg
20 25 30

<210> 1417
<211> 20
<212> PRT
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<220>
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<400> 1417

Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr
1 5 10 15

Ile Gly Ser Arg
20

<210> 1418
<211> 45
<212> PRT
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<220>
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<400> 1418

Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr
1 5 10 15

Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile
20 25 30

Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg
35 40 45

<210> 1419
<211> 80
<212> PRT
<213> Artificial sequence

<220>
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<400> 1419

Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr
1 5 10 15

Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile
20 25 30

Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly
35 40 45

Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser
50 55 60

Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg
65 70 75 80

<210> 1420
<211> 125
<212> PRT
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<220>
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<400> 1420

Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr
1 5 10 15

Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile
20 25 30

Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly
35 40 45

Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser
50 55 60

Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg
65 70 75 80

Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr
85 90 95

Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile
100 105 110

Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg
115 120 125

<210> 1421
<211> 20
<212> PRT
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<220>
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<400> 1421

Ile Pro Cys Asn Asn Lys Gly Ala His Ser Val Gly Leu Met Trp Trp
1 5 10 15

Met Leu Ala Arg
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<210> 1422
<211> 19
<212> PRT
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<220>
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<400> 1422

Tyr Ile Gly Ser Arg Arg Glu Asp Val Glu Ile Leu Asp Val Pro Asp
1 5 10 15

Ser Gly Arg

<210> 1423
<211> 14
<212> PRT
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<220>
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<400> 1423

Arg Gly Asp Arg Gly Asp Tyr Ile Gly Ser Arg Arg Gly Asp
1 5 10

<210> 1424
<211> 25
<212> PRT
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<220>
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<400> 1424

Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr Ile Gly Ser Arg Tyr
1 5 10 15

Ile Gly Ser Arg Tyr Ile Gly Ser Arg
20 25

<210> 1425
<211> 19
<212> PRT
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<220>
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<400> 1425

Arg Glu Asp Val Glu Ile Leu Asp Val Tyr Ile Gly Ser Arg Pro Asp
1 5 10 15

Ser Gly Arg

<210> 1426
<211> 19
<212> PRT
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<220>
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<400> 1426

Tyr Ile Gly Ser Arg Arg Glu Asp Val Glu Ile Leu Asp Val Pro Asp
1 5 10 15

Ser Gly Arg

<210> 1427
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 1427

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> 1428
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1428

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> 1429
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1429

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> 1430
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1430

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> 1431
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 1431

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> 1432

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

<220>
<223> Synthetic peptide

<400> 1432

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> 1433
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 1433

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> 1434
<211> 20
<212> PRT
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<220>
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<400> 1434

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> 1435
<211> 20
<212> PRT
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<220>
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<400> 1435

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> 1436
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 1436

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> 1437
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 1437

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> 1438
<211> 20
<212> PRT
<213> Artificial sequence

<220>
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<400> 1438

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> 1439
<211> 20
<212> PRT
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<220>
<223> Synthetic peptide

<400> 1439

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> 1440
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1440

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> 1441
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1441

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> 1442
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1442

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> 1443
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1443

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> 1444
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1444

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> 1445
<211> 20
<212> PRT
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<220>
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<400> 1445

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> 1446
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1446

Ile His Gly Cys Trp Phe Thr Glu Glu Gly Cys Val Trp Gln
1 5 10

<210> 1447
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1447

Tyr Met Gln Cys Gln Phe Ala Arg Asp Gly Cys Pro Gln Trp
1 5 10

<210> 1448
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1448

Lys Leu Gln Cys Gln Tyr Ser Glu Ser Gly Cys Pro Thr Ile
1 5 10

<210> 1449
<211> 14
<212> PRT
<213> Artificial sequence

<220>
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<400> 1449

Phe Leu Gln Cys Glu Ile Ser Gly Gly Ala Cys Pro Ala Pro
1 5 10

<210> 1450
<211> 14
<212> PRT
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<220>
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<400> 1450

Lys Leu Gln Cys Glu Phe Ser Thr Ser Gly Cys Pro Asp Leu
1 5 10

<210> 1451
<211> 14
<212> PRT
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<220>
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<400> 1451

Lys Leu Gln Cys Glu Phe Ser Thr Gln Gly Cys Pro Asp Leu
1 5 10

<210> 1452
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<212> PRT
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<220>
<223> Synthetic peptide

<400> 1452

Lys Leu Gln Cys Glu Phe Ser Thr Ser Gly Cys Pro Trp Leu
1 5 10

<210> 1453
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1453

Ile Gln Gly Cys Trp Phe Thr Glu Glu Gly Cys Pro Trp Gln
1 5 10

<210> 1454
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1454

Ser Phe Asp Cys Asp Asn Pro Trp Gly His Val Leu Gln Ser Cys Phe
1 5 10 15

Gly Phe

<210> 1455
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1455

Ser Phe Asp Cys Asp Asn Pro Trp Gly His Lys Leu Gln Ser Cys Phe
1 5 10 15

Gly Phe

<210> 1456
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> BINDING
<222> (18)..(18)
<223> Linker protein bound to residue 18

<400> 1456

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu

<210> 1457
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Linker protein bound to residue 1

<400> 1457

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu

<210> 1458
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (18)..(19)
<223> Linker protein between residues 18 and 19

<220>
<221> Binding
<222> (36)..(36)
<223> Linker protein bound to residue 36

<400> 1458

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val
20 25 30

Cys Asp Pro Leu
35

<210> 1459
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (1)..(1)
<223> Linker protein bound to residue 1

<220>
<221> Misc_feature
<222> (18)..(19)
<223> Linker protein between residues 18 and 19

<400> 1459

Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp
1 5 10 15

Pro Leu Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val
20 25 30

Cys Asp Pro Leu
35

<210> 1460
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (18)..(18)
<223> Linker protein bound to residue 18

<400> 1460

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser

<210> 1461
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (1)..(1)
<223> Linker protein bound to residue 1

<400> 1461

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys Thr
1 5 10 15

Ser Ser

<210> 1462
<211> 34
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (17)..(18)
<223> Linker protein between residues 17 and 18

<220>
<221> Binding
<222> (34)..(34)
<223> Linker protein bound to residue 34

<400> 1462

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr Ser
1 5 10 15

Ser Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr
20 25 30

Ser Ser

<210> 1463
<211> 34
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (1)..(1)
<223> Linker protein bound to residue 1

<220>
<221> Misc_feature
<222> (17)..(18)
<223> Linker protein between residues 17 and 18

<400> 1463

Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr Ser

1 5 10 15

Ser Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Thr
20 25 30

Ser Ser

<210> 1464
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (18)..(18)
<223> Linker protein bound to residue 18

<400> 1464

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu

<210> 1465
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (1)..(1)
<223> Linker protein bound to residue 1

<400> 1465

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu

<210> 1466
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Misc_feature
<222> (18)..(19)
<223> Linker protein between residues 18 and 19

<220>
<221> Binding
<222> (36)..(36)
<223> Linker protein bound to residue 36

<400> 1466

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val
20 25 30

Cys His Gly Leu
35

<210> 1467
<211> 36
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<220>
<221> Binding
<222> (1)..(1)
<223> Linker protein bound to residue 1

<220>
<221> Misc_feature
<222> (18)..(19)
<223> Linker protein between residues 18 and 19

<400> 1467

Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys His
1 5 10 15

Gly Leu Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val
20 25 30

Cys His Gly Leu
35

<210> 1468
<211> 248
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1468

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

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35 40 45

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

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

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

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu 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> 1469
<211> 248
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1469

```
Met Trp Gly Ala Cys Trp Pro Phe Pro Trp Glu Cys Phe Lys Glu Gly
1               5                  10                  15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
            20                  25                  30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
        35                  40                  45

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65                  70                  75                  80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
                85                  90                  95

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

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

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu 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> 1470
<211> 248
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1470

Met Val Pro Phe Cys Asp Leu Leu Thr Lys His Cys Phe Glu Ala Gly
1 5 10 15

Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
20 25 30

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
35 40 45

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

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
65 70 75 80

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
85 90 95

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

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

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

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu 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> 1471
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1471

Met Gly Ser Arg Cys Lys Tyr Lys Trp Asp Val Leu Thr Lys Gln Cys
1 5 10 15

Phe His His Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu 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> 1472
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1472

```
Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1               5                   10                  15

Asp Pro Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
            20                  25                  30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        35                  40                  45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65                  70                  75                  80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                85                  90                  95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            100                 105                 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    130                 135                 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145                 150                 155                 160

Asp Glu Leu 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> 1473
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1473

Met Ser Ala Asp Cys Tyr Phe Asp Ile Leu Thr Lys Ser Asp Val Cys
1 5 10 15

Thr Ser Ser Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
115 120 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

```
Asp Glu Leu 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> 1474
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1474

```
Met Ser Asp Asp Cys Met Tyr Asp Gln Leu Thr Arg Met Phe Ile Cys
1               5                   10                  15

Ser Asn Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
            20                  25                  30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        35                  40                  45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65                  70                  75                  80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                85                  90                  95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            100                 105                 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125
```

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
130 135 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145 150 155 160

Asp Glu Leu 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> 1475
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1475

Met Asp Leu Asn Cys Lys Tyr Asp Glu Leu Thr Tyr Lys Glu Trp Cys
1 5 10 15

Gln Phe Asn Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
20 25 30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
35 40 45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65 70 75 80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
85 90 95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
100 105 110

```
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    130                 135                 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145                 150                 155                 160

Asp Glu Leu 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> 1476
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1476

```
Met Phe His Asp Cys Lys Tyr Asp Leu Leu Thr Arg Gln Met Val Cys
1               5                   10                  15

His Gly Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
            20                  25                  30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        35                  40                  45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65                  70                  75                  80
```

```
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                85                  90                  95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            100                 105                 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    130                 135                 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145                 150                 155                 160

Asp Glu Leu 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> 1477
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1477

```
Met Arg Asn His Cys Phe Trp Asp His Leu Leu Lys Gln Asp Ile Cys
1               5                   10                  15

Pro Ser Pro Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
            20                  25                  30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        35                  40                  45

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    50                  55                  60
```

```
Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65                  70                  75                  80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                85                  90                  95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            100                 105                 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    130                 135                 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145                 150                 155                 160

Asp Glu Leu 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> 1478
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1478

```
Met Ala Asn Gln Cys Trp Trp Asp Ser Leu Thr Lys Lys Asn Val Cys
1               5                   10                  15

Glu Phe Phe Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
            20                  25                  30
```

```
Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        35                  40                  45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65                  70                  75                  80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                85                  90                  95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            100                 105                 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    130                 135                 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145                 150                 155                 160

Asp Glu Leu 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> 1479
<211> 252
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1479

```
Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1               5                   10                  15
```

```
His Gly Leu Gly Gly Gly Gly Gly Val Asp Lys Thr His Thr Cys Pro
            20                  25                  30

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        35                  40                  45

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

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
65                  70                  75                  80

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                85                  90                  95

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
            100                 105                 110

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        115                 120                 125

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    130                 135                 140

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
145                 150                 155                 160

Asp Glu Leu 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
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<210> 1480
<211> 293
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1480

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Met Leu Pro Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys
1               5                  10                  15

Asp Pro Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
            20                  25                  30

Ser Ser Gly Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp
        35                  40                  45

Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly Gly
    50                  55                  60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
65                  70                  75                  80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                85                  90                  95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            100                 105                 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        115                 120                 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    130                 135                 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
145                 150                 155                 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                165                 170                 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            180                 185                 190

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

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    210                 215                 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
225                 230                 235                 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                245                 250                 255
```

```
Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            260                 265                 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        275                 280                 285

Leu Ser Pro Gly Lys
    290
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<210> 1481
<211> 293
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1481

```
Met Phe His Asp Cys Lys Trp Asp Leu Leu Thr Lys Gln Trp Val Cys
1               5                   10                  15

His Gly Leu Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala
            20                  25                  30

Ser Ser Gly Ser Gly Ser Ala Thr His Met Phe His Asp Cys Lys Trp
        35                  40                  45

Asp Leu Leu Thr Lys Gln Trp Val Cys His Gly Leu Gly Gly Gly Gly
    50                  55                  60

Gly Val Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
65                  70                  75                  80

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                85                  90                  95

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            100                 105                 110

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        115                 120                 125

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    130                 135                 140

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
145                 150                 155                 160

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                165                 170                 175

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            180                 185                 190
```

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

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    210                 215                 220

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
225                 230                 235                 240

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                245                 250                 255

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            260                 265                 270

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        275                 280                 285

Leu Ser Pro Gly Lys
    290
```

<210> 1482
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1482

```
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> 1483
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1483

```
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> 1484
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1484

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> 1485
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1485

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> 1486
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1486

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> 1487
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1487

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> 1488
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1488

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> 1489
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1489

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> 1490
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1490

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> 1491
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1491

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> 1492
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1492

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> 1493
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1493

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> 1494
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1494

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> 1495
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1495

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> 1496
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1496

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> 1497
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1497

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> 1498
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1498

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> 1499
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1499

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> 1500
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1500

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> 1501
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1501

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> 1502
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1502

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> 1503
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1503

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> 1504
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1504

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> 1505
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1505

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> 1506
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1506

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> 1507
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1507

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> 1508
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1508

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> 1509
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1509

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> 1510
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1510

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> 1511
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1511

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> 1512
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1512

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> 1513
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1513

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> 1514
<211> 20
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1514

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> 1515
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1515

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> 1516
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1516

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> 1517
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1517

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> 1518
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1518

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> 1519
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1519

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> 1520
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1520

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> 1521
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1521

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> 1522
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1522

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> 1523
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1523

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> 1524
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1524

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> 1525
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1525

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

<210> 1526
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1526

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> 1527
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1527

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> 1528
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1528

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> 1529
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1529

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> 1530
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1530

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> 1531
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1531

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> 1532
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1532

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> 1533
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1533

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> 1534
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1534

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> 1535
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1535

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> 1536
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1536

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> 1537
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1537

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> 1538
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1538

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> 1539
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1539

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> 1540
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1540

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> 1541
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1541

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> 1542
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1542

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> 1543
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1543

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> 1544
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1544

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> 1545
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1545

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> 1546
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1546

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> 1547
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1547

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> 1548
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1548

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> 1549
<211> 22
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1549

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> 1550
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1550

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> 1551
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1551

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> 1552
<211> 20
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1552

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> 1553
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1553

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> 1554
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1554

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> 1555
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1555

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> 1556
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1556

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> 1557
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1557

Lys Arg Pro Cys Glu Glu Ile Phe Gly Gly Cys Thr Tyr Gln
1 5 10

<210> 1558
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1558

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> 1559
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1559

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> 1560
<211> 20

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1560

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> 1561
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1561

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> 1562
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1562

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> 1563
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1563

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> 1564
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1564

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> 1565
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1565

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> 1566
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1566

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> 1567
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1567

Phe Asp Tyr Cys Glu Gly Val Glu Asp Pro Phe Thr Phe Gly Cys Asp
1 5 10 15

Asn His

<210> 1568
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1568

Lys Arg Pro Cys Glu Glu Met Trp Gly Gly Cys Asn Tyr Asp
1 5 10

<210> 1569
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1569

His Gln Ile Cys Lys Trp Asp Pro Trp Thr Cys Lys His Trp
1 5 10

<210> 1570
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1570

Lys Arg Pro Cys Glu Glu Ile Phe Gly Gly Cys Thr Tyr Gln
1 5 10

<210> 1571
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1571

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

<210> 1572
<211> 18
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1572

Phe Asp Tyr Cys Glu Gly Val Glu Asp Pro Phe Thr Phe Gly Cys Asp
1 5 10 15

Asn His

<210> 1573
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1573

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> 1574
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1574

Gln Tyr Gly Cys Asp Gly Phe Leu Tyr Gly Cys Met Ile Asn
1 5 10

<210> 1575
<211> 31
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1575

Met Gly Ala Gln Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu
1 5 10 15

Tyr Glu Gln Phe Thr Phe Gln Gln Leu Glu Gly Gly Gly Gly Gly
20 25 30

<210> 1576
<211> 28
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1576

Met Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln
1 5 10 15

Phe Thr Phe Gln Gln Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1577
<211> 50
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1577

Met Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln
1 5 10 15

Phe Thr Phe Gln Gln Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser
20 25 30

Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr His Leu Glu Gly Gly Gly
35 40 45

Gly Gly
50

<210> 1578
<211> 59
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1578

Met Gly Ala Gln Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu
1 5 10 15

Tyr Glu Gln Phe Thr Phe Gln Gln Gly Gly Gly Gly Gly Gly Gly Gly
20 25 30

Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln Phe
35 40 45

Thr Phe Gln Gln Leu Glu Gly Gly Gly Gly Gly
50 55

<210> 1579
<211> 55
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1579

Met Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln
1 5 10 15

Phe Thr Phe Gln Gln Gly Gly Gly Gly Gly Gly Gly Lys Phe Asn Pro
20 25 30

Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln Phe Thr Phe Gln Gln
35 40 45

Leu Glu Gly Gly Gly Gly Gly
50 55

<210> 1580
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1580

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

His Met Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1581
<211> 44
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1581

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

Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser
20 25 30

Gly Ser Ala Thr His Leu Glu Gly Gly Gly Gly Gly
35 40

<210> 1582
<211> 61
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1582

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

His Met Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser
20 25 30

Ser Gly Ser Gly Ser Ala Thr His Gln Glu Glu Cys Glu Trp Asp Pro
35 40 45

Trp Thr Cys Glu His Met Leu Glu Gly Gly Gly Gly Gly
50 55 60

<210> 1583
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1583

Gly Gly Gly Gly Gly Ala Gln Lys Phe Asn Pro Leu Asp Glu Leu Glu
1 5 10 15

Glu Thr Leu Tyr Glu Gln Phe Thr Phe Gln Gln Leu Glu
20 25

<210> 1584
<211> 51
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1584

Gly Gly Gly Gly Gly Ala Gln Gly Ser Gly Ser Ala Thr Gly Gly Ser
1 5 10 15

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr His Lys Phe Asn
20 25 30

Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln Phe Thr Phe Gln
35 40 45

Gln Leu Glu
50

<210> 1585
<211> 57
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1585

Gly Gly Gly Gly Gly Ala Gln Lys Phe Asn Pro Leu Asp Glu Leu Glu
1 5 10 15

Glu Thr Leu Tyr Glu Gln Phe Thr Phe Gln Gln Gly Gly Gly Gly Gly
20 25 30

Gly Gly Gly Lys Phe Asn Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr
35 40 45

Glu Gln Phe Thr Phe Gln Gln Leu Glu
50 55

<210> 1586
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1586

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

Thr Cys Glu His Met Leu Glu
20

<210> 1587
<211> 45
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1587

Gly Gly Gly Gly Gly Ala Gln Gly Ser Gly Ser Ala Thr Gly Gly Ser
1 5 10 15

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr His Gln Glu Glu
20 25 30

Cys Glu Trp Asp Pro Trp Thr Cys Glu His Met Leu Glu
35 40 45

<210> 1588
<211> 59
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1588

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

Thr Cys Glu His Met Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser
20 25 30

Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr His Gln Glu Glu Cys Glu
35 40 45

Trp Asp Pro Trp Thr Cys Glu His Met Leu Glu
50 55

<210> 1589
<211> 74
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1589

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

Met Gly Gly Gly Gly Gly Gly Gly Gly Lys Phe Asn Pro Leu Asp Glu
20 25 30

Leu Glu Glu Thr Leu Tyr Glu Gln Phe Thr Phe Gln Gln Gly Ser Gly
35 40 45

Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser
50 55 60

Ala Thr His Leu Glu Gly Gly Gly Gly Gly
65 70

<210> 1590
<211> 70
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1590

Gly Gly Gly Gly Gly Ala Gln Gly Ser Gly Ser Ala Thr Gly Gly Ser
1 5 10 15

Gly Ser Thr Ala Ser Ser Gly Ser Gly Ser Ala Thr His Lys Phe Asn
20 25 30

Pro Leu Asp Glu Leu Glu Glu Thr Leu Tyr Glu Gln Phe Thr Phe Gln
35 40 45

Gln Gly Gly Gly Gly Gly Gln Glu Glu Cys Glu Trp Asp Pro Trp Thr
50 55 60

Cys Glu His Met Leu Glu
65 70

<210> 1591
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1591

Met Gly Ala Gln Phe Asp Tyr Cys Glu Gly Val Glu Asp Pro Phe Thr
1 5 10 15

Phe Gly Cys Asp Asn His Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1592
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1592

Met Gly Ala Gln Gln Tyr Gly Cys Asp Gly Phe Leu Tyr Gly Cys Met
1 5 10 15

Ile Asn Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1593
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1593

Met Gly Ala Gln Lys Arg Pro Cys Glu Glu Met Trp Gly Gly Cys Asn
1 5 10 15

Tyr Asp Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1594
<211> 25

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1594

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

His Trp Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1595
<211> 25
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1595

Met Gly Ala Gln Lys Arg Pro Cys Glu Glu Ile Phe Gly Gly Cys Thr
1 5 10 15

Tyr Gln Leu Glu Gly Gly Gly Gly Gly
20 25

<210> 1596
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1596

Gly Gly Gly Gly Gly Ala Gln Pro Ile Arg Gln Glu Glu Cys Asp Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Trp Glu Val Leu Glu
20 25

<210> 1597
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1597

Gly Gly Gly Gly Gly Ala Gln Thr Asn Ile Gln Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Asp His Met Pro Gly Lys Leu Glu
20 25

<210> 1598
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1598

Gly Gly Gly Gly Gly Ala Gln Trp Tyr Glu Gln Asp Ala Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Ala Glu Val Leu Glu
20 25

<210> 1599
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1599

Gly Gly Gly Gly Gly Ala Gln Asn Arg Leu Gln Glu Val Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Glu Asn Val Leu Glu
20 25

<210> 1600
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1600

Gly Gly Gly Gly Gly Ala Gln Ala Ala Thr Gln Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Pro Arg Ser Leu Glu
20 25

<210> 1601
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1601

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

Asp Pro Trp Thr Cys Glu His Met Phe Asp Trp Leu Glu
20 25

<210> 1602
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1602

Gly Gly Gly Gly Gly Ala Gln Val Pro Arg Gln Lys Asp Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Tyr Val Gly Leu Glu
20 25

<210> 1603
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1603

Gly Gly Gly Gly Gly Ala Gln Ser Ile Ser His Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Gln Val Gly Leu Glu
20 25

<210> 1604
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1604

Gly Gly Gly Gly Gly Ala Gln Trp Ala Ala Gln Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Gly Arg Met Leu Glu
20 25

<210> 1605
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1605

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

Asp Pro Trp Thr Cys Glu His Met Gly Ser Thr Leu Glu
20 25

<210> 1606
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1606

Gly Gly Gly Gly Gly Ala Gln Gly His Ser Gln Glu Glu Cys Gly Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Gly Thr Ser Leu Glu
20 25

<210> 1607
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1607

Gly Gly Gly Gly Gly Ala Gln Gln His Trp Gln Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Asp His Met Pro Ser Lys Leu Glu
20 25

<210> 1608
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1608

Gly Gly Gly Gly Gly Ala Gln Asn Val Arg Gln Glu Lys Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Pro Val Arg Leu Glu
20 25

<210> 1609
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1609

Gly Gly Gly Gly Gly Ala Gln Lys Ser Gly Gln Val Glu Cys Asn Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Pro Arg Asn Leu Glu
20 25

<210> 1610
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1610

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

Asp Pro Trp Thr Cys Glu His Met Arg Glu Trp Leu Glu
20 25

<210> 1611
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1611

Gly Gly Gly Gly Gly Ala Gln Ala Trp Gly Gln Glu Gly Cys Asp Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Leu Pro Met Leu Glu
20 25

<210> 1612
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1612

Gly Gly Gly Gly Gly Ala Gln Pro Val Asn Gln Glu Asp Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Pro Pro Met Leu Glu
20 25

<210> 1613
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1613

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

Asp Pro Trp Thr Cys Ala His Met Asp Ile Lys Leu Glu
20 25

<210> 1614
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1614

Gly Gly Gly Gly Gly Ala Gln His Gly Gln Asn Met Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Phe Arg Tyr Leu Glu
20 25

<210> 1615
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1615

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

Asp Pro Trp Thr Cys Glu His Met Pro Leu Arg Leu Glu
20 25

<210> 1616
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1616

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

Asp Pro Trp Thr Cys Glu His Met Glu Ser Gln Leu Glu
20 25

<210> 1617
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1617

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

Asp Pro Trp Thr Cys Asp His Met Val Ser Ser Leu Glu
20 25

<210> 1618
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1618

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

Asp Pro Trp Thr Cys Glu His Leu Glu Gly Leu Leu Glu
20 25

<210> 1619
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1619

Gly Gly Gly Gly Gly Ala Gln Trp Ala Gln Gln Glu Glu Cys Ala Trp
1 5 10 15

Asp Pro Trp Thr Cys Asp His Met Val Gly Leu Leu Glu
20 25

<210> 1620
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1620

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

Asp Pro Trp Thr Cys Glu His Met Val Arg Ser Leu Glu
20 25

<210> 1621
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1621

Gly Gly Gly Gly Gly Ala Gln Pro Met Asn Gln Val Glu Cys Asp Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Pro Arg Ser Leu Glu
20 25

<210> 1622
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1622

Gly Gly Gly Gly Gly Ala Gln Phe Gly Trp Ser His Gly Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Gly Ser Thr Leu Glu
20 25

<210> 1623
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1623

Gly Gly Gly Gly Gly Ala Gln Lys Ser Thr Gln Asp Asp Cys Asp Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Val Gly Pro Leu Glu
20 25

<210> 1624
<211> 29
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1624

Gly Gly Gly Gly Gly Ala Gln Gly Pro Arg Ile Ser Thr Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu His Met Asp Gln Leu Leu Glu
20 25

<210> 1625
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1625

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

Asp Pro Trp Thr Cys Ala His Met Gln Val Asp Leu Glu
20 25

<210> 1626
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1626

Gly Gly Gly Gly Gly Ala Gln Val Leu Gly Gly Gln Gly Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Arg Leu Leu Gln Gly Trp Leu Glu
20 25

<210> 1627
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1627

Gly Gly Gly Gly Gly Ala Gln Val Leu Gly Gly Gln Gly Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Ser His Leu Glu Asp Gly Leu Glu
20 25

<210> 1628
<211> 29

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1628

Gly Gly Gly Gly Gly Ala Gln Thr Thr Ile Gly Ser Met Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Ala His Met Gln Gly Gly Leu Glu
20 25

<210> 1629
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1629

Gly Gly Gly Gly Gly Ala Gln Thr Lys Gly Lys Ser Val Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Ser His Met Gln Ser Gly Leu Glu
20 25

<210> 1630
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1630

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

Asp Pro Trp Thr Cys Ala His Met Gln Gly Gly Leu Glu
20 25

<210> 1631
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1631

Gly Gly Gly Gly Gly Ala Gln Trp Val Asn Glu Val Val Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Asn His Trp Asp Thr Pro Leu Glu
20 25

<210> 1632
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1632

Gly Gly Gly Gly Gly Ala Gln Val Val Gln Val Gly Met Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Lys His Met Arg Leu Gln Leu Glu
20 25

<210> 1633
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1633

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

Asp Pro Trp Thr Cys Ala His Leu Val Glu Val Leu Glu
20 25

<210> 1634
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1634

Gly Gly Gly Gly Gly Ala Gln Gln Gly Met Lys Met Phe Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Ala His Ile Val Tyr Arg Leu Glu
20 25

<210> 1635
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1635

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

Asp Pro Trp Thr Cys Glu His Met Gln Gly Gly Leu Glu
20 25

<210> 1636
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1636

Gly Gly Gly Gly Gly Ala Gln Thr Ser Gln Arg Val Gly Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Gln His Leu Thr Tyr Thr Leu Glu
20 25

<210> 1637
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1637

Gly Gly Gly Gly Gly Ala Gln Gln Trp Ser Trp Pro Pro Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Gln Thr Val Trp Pro Ser Leu Glu
20 25

<210> 1638
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1638

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

Asp Pro Trp Thr Cys Ser His Met Val Gln Gly Leu Glu
20 25

<210> 1639
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1639

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

Asp Pro Trp Thr Cys Lys Val Leu Trp Pro Ser Leu Glu
20 25

<210> 1640
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1640

Gly Gly Gly Gly Gly Ala Gln Val Trp Arg Ser Gln Val Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Asn Leu Gly Gly Asp Trp Leu Glu
20 25

<210> 1641
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1641

Gly Gly Gly Gly Gly Ala Gln Asp Lys Ile Leu Glu Glu Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Gln Phe Phe Tyr Gly Ala Leu Glu
20 25

<210> 1642
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1642

Gly Gly Gly Gly Gly Ala Gln Ala Thr Phe Ala Arg Gln Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Ala Leu Gly Gly Asn Trp Leu Glu
20 25

<210> 1643
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1643

Gly Gly Gly Gly Gly Ala Gln Gly Pro Ala Gln Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Glu Pro Leu Pro Leu Met Leu Glu
20 25

<210> 1644
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1644

Gly Gly Gly Gly Gly Ala Gln Arg Pro Glu Asp Met Cys Ser Gln Trp
1 5 10 15

Asp Pro Trp Thr Trp His Leu Gln Gly Tyr Cys Leu Glu
20 25

<210> 1645
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1645

Gly Gly Gly Gly Gly Ala Gln Leu Trp Gln Leu Ala Val Cys Gln Trp
1 5 10 15

Asp Pro Gln Thr Cys Asp His Met Gly Ala Leu Leu Glu
20 25

<210> 1646
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1646

Gly Gly Gly Gly Gly Ala Gln Thr Gln Leu Val Ser Leu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Arg Leu Leu Asp Gly Trp Leu Glu
20 25

<210> 1647
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1647

Gly Gly Gly Gly Gly Ala Gln Met Gly Gly Ala Gly Arg Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Gln Leu Leu Gln Gly Trp Leu Glu
20 25

<210> 1648
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1648

Gly Gly Gly Gly Gly Ala Gln Met Phe Leu Pro Asn Glu Cys Gln Trp
1 5 10 15

Asp Pro Trp Thr Cys Ser Asn Leu Pro Glu Ala Leu Glu
20 25

<210> 1649
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1649

Gly Gly Gly Gly Gly Ala Gln Phe Gly Trp Ser His Gly Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Arg Leu Leu Gln Gly Trp Leu Glu
20 25

<210> 1650
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1650

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

Asp Pro Trp Thr Cys Arg Leu Leu His Gly Trp Leu Glu
20 25

<210> 1651
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1651

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

Asp Pro Trp Thr Cys Arg Leu Tyr Gly Met Trp Leu Glu
20 25

<210> 1652
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1652

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

Asp Pro Trp Thr Cys Arg Leu Leu Gln Gly Trp Leu Glu
20 25

<210> 1653
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1653

Gly Gly Gly Gly Gly Ala Gln Asp Lys Ile Leu Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Arg Leu Leu Gln Gly Trp Leu Glu
20 25

<210> 1654
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1654

Gly Gly Gly Gly Gly Ala Gln Ala Ala Thr Gln Glu Glu Cys Glu Trp
1 5 10 15

Asp Pro Trp Thr Cys Arg Leu Leu Gln Gly Trp Leu Glu
20 25

<210> 1655
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1655

Met Gly Ala Gln Thr Asn Phe Met Pro Met Asp Asp Leu Glu Gln Arg
1 5 10 15

Leu Tyr Glu Gln Phe Ile Leu Gln Gln Gly Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1656
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1656

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

Leu Tyr Glu His Trp Ile Leu Gln His Ser Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1657
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1657

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

Leu Tyr Asp Gln Phe Met Leu Gln Gln Gly Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1658
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1658

Met Gly Ala Gln Leu Asn Phe Thr Pro Leu Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Gln Trp Thr Leu Gln Gln Ser Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1659
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1659

Met Gly Ala Gln Gln Lys Phe Gln Pro Leu Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Gln Phe Met Leu Gln Gln Ala Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1660
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1660

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

Leu Tyr Asn Gln Trp Met Phe His Gln Arg Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1661
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1661

Met Gly Ala Gln Val Lys Tyr Lys Pro Leu Asp Glu Leu Asp Glu Ile
1 5 10 15

Leu Tyr Glu Gln Gln Thr Phe Gln Glu Arg Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1662
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1662

Met Gly Ala Gln Thr Lys Phe Gln Pro Leu Asp Glu Leu Asp Gln Thr
1 5 10 15

Leu Tyr Glu Gln Trp Thr Leu Gln Gln Arg Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1663
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1663

Met Gly Ala Gln Thr Asn Phe Gln Pro Leu Asp Glu Leu Asp Gln Thr
1 5 10 15

Leu Tyr Glu Gln Trp Thr Leu Gln Gln Arg Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1664
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1664

Met Gly Ala Gln Gln Asn Phe Lys Pro Met Asp Glu Leu Glu Asp Thr
1 5 10 15

Leu Tyr Lys Gln Phe Leu Phe Gln His Ser Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1665
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1665

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

Leu Tyr His Gln Phe Thr Leu His His Gln Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1666
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1666

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

Leu Tyr Glu Gln Trp Thr Leu Gln His Val Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1667
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1667

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

Leu Tyr Glu His Phe Ile Phe His Tyr Thr Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1668
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1668

Met Gly Ala Gln Val Lys Phe Lys Pro Leu Asp Ala Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu His Trp Met Phe Gln Gln Ala Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1669
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1669

Met Gly Ala Gln Glu Asp Tyr Met Pro Leu Asp Ala Leu Asp Ala Gln
1 5 10 15

Leu Tyr Glu Gln Phe Ile Leu Leu His Gly Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1670
<211> 33

<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1670

Met Gly Ala Gln Tyr Lys Phe Asn Pro Met Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Glu Phe Leu Phe Gln His Ala Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1671
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1671

Met Gly Ala Gln Ser Asn Phe Met Pro Leu Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Gln Phe Met Leu Gln His Gln Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1672
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1672

Met Gly Ala Gln Gln Lys Phe Gln Pro Leu Asp Glu Leu Glu Glu Thr
1 5 10 15

Leu Tyr Lys Gln Trp Thr Leu Gln Gln Arg Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1673
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1673

Met Gly Ala Gln Gln Lys Phe Met Pro Leu Asp Glu Leu Asp Glu Ile
1 5 10 15

Leu Tyr Glu Gln Phe Met Phe Gln Gln Ser Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1674
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1674

Met Gly Ala Gln Thr Lys Phe Asn Pro Leu Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Gln Trp Thr Leu Gln His Gln Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1675
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1675

Met Gly Ala Gln His Thr Phe Gln Pro Leu Asp Glu Leu Glu Glu Thr
1 5 10 15

Leu Tyr Tyr Gln Trp Leu Tyr Asp Gln Leu Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1676
<211> 33
<212> PRT
<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 1676

Met Gly Ala Gln Gln Lys Phe Lys Pro Leu Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Gln Trp Thr Leu Gln Gln Arg Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1677
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1677

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

Leu Tyr Glu Gln Trp Ile Arg Arg Tyr His Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1678
<211> 33
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1678

Met Gly Ala Gln Ser Lys Phe Lys Pro Leu Asp Glu Leu Glu Gln Thr
1 5 10 15

Leu Tyr Glu Gln Trp Thr Leu Gln His Ala Leu Glu Gly Gly Gly Gly
20 25 30

Gly

<210> 1679
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1679

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

Ile Phe Gly Cys Gly Thr Gln Asn Leu Ala Leu Leu Glu
20 25

<210> 1680
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1680

Gly Gly Gly Gly Gly Ala Gln Ala Gly Gly Met Arg Pro Tyr Asp Gly
1 5 10 15

Met Leu Gly Trp Pro Asn Tyr Asp Val Gln Ala Leu Glu
20 25

<210> 1681
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1681

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

Met Phe Gly Cys Gly Thr Lys Asp Trp Tyr Gly Leu Glu
20 25

<210> 1682
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1682

Gly Gly Gly Gly Gly Ala Gln Ala Pro Gly Gln Arg Pro Tyr Asp Gly
1 5 10 15

Met Leu Gly Trp Pro Thr Tyr Gln Arg Ile Val Leu Glu
20 25

<210> 1683
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1683

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

Ile Leu Gly Pro Val Thr Trp Arg Arg Cys Ile Leu Glu
20 25

<210> 1684
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1684

Gly Gly Gly Gly Gly Ala Gln Phe Gly Asp Lys Arg Pro Leu Glu Cys
1 5 10 15

Met Phe Gly Gly Pro Ile Gln Leu Cys Pro Arg Leu Glu
20 25

<210> 1685
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1685

Gly Gly Gly Gly Gly Ala Gln Lys Arg Pro Cys Glu Glu Ile Phe Gly
1 5 10 15

Gly Cys Thr Tyr Gln Leu Glu
20

<210> 1686
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1686

Gly Gly Gly Gly Gly Ala Gln Leu Gln Glu Trp Cys Glu Gly Val Glu
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Glu Lys Gln Arg Leu Glu
20 25

<210> 1687
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1687

Gly Gly Gly Gly Gly Ala Gln Met Leu Asp Tyr Cys Glu Gly Met Asp
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Asp Lys Gln Met Leu Glu
20 25

<210> 1688
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1688

Gly Gly Gly Gly Gly Ala Gln His Gln Glu Tyr Cys Glu Gly Met Glu
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Glu Tyr Gln Gly Leu Glu
20 25

<210> 1689
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1689

Gly Gly Gly Gly Gly Ala Gln Leu Gln Asp Tyr Cys Glu Gly Val Glu
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Glu Asn Gln Arg Leu Glu
20 25

<210> 1690
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1690

Gly Gly Gly Gly Gly Ala Gln Leu Leu Asp Tyr Cys Glu Gly Val Gln
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Glu Asn Leu Asp Leu Glu
20 25

<210> 1691
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1691

Gly Gly Gly Gly Gly Ala Gln Gly Phe Glu Tyr Cys Asp Gly Met Glu
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Asp Lys Gln Thr Leu Glu
20 25

<210> 1692
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1692

Gly Gly Gly Gly Gly Ala Gln Ala Gln Asp Tyr Cys Glu Gly Met Glu
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Glu Met Gln Lys Leu Glu
20 25

<210> 1693
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1693

Gly Gly Gly Gly Gly Ala Gln Leu Gln Asp Tyr Cys Glu Gly Val Glu
1 5 10 15

Asp Pro Phe Thr Phe Gly Cys Glu Lys Gln Arg Leu Glu
20 25

<210> 1694
<211> 29
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1694

Gly Gly Gly Gly Gly Ala Gln Lys Leu Glu Tyr Cys Asp Gly Met Glu
1 5 10 15

Asp Pro Phe Thr Gln Gly Cys Asp Asn Gln Ser Leu Glu
20 25

<210> 1695
<211> 27
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1695

Gly Gly Gly Gly Gly Ala Gln Phe Asp Tyr Cys Glu Gly Val Glu Asp
1 5 10 15

Pro Phe Thr Phe Gly Cys Asp Asn His Leu Glu
20 25

<210> 1696
<211> 228
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1696

Val 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
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<210> 1697
<211> 62
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1697

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Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu
1               5                   10                  15

Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
            20                  25                  30

Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp Asp Leu Leu
        35                  40                  45

Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly Gly Gly
    50                  55                  60
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<210> 1698
<211> 290
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1698

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Gly Cys Lys Trp Asp Leu Leu Ile Lys Gln Trp Val Cys Asp Pro Leu
1               5                   10                  15
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Gly Ser Gly Ser Ala Thr Gly Gly Ser Gly Ser Thr Ala Ser Ser Gly
            20                  25                  30

Ser Gly Ser Ala Thr His Met Leu Pro Gly Cys Lys Trp Asp Leu Leu
        35                  40                  45

Ile Lys Gln Trp Val Cys Asp Pro Leu Gly Gly Gly Gly Gly Val Asp
    50                  55                  60

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
65                  70                  75                  80

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                85                  90                  95

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            100                 105                 110

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        115                 120                 125

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    130                 135                 140

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
145                 150                 155                 160

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                165                 170                 175

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

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

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    210                 215                 220

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
225                 230                 235                 240

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                245                 250                 255

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            260                 265                 270

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        275                 280                 285
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Gly Lys
290

<210> 1699
<211> 228
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1699

Val 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> 1700
<211> 27
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1700

Gly Gly Gly Gly Gly Ala Gln Leu Ala Asp His Gly Gln Cys Ile Arg
1 5 10 15

Trp Pro Trp Met Cys Pro Pro Glu Gly Trp Glu
20 25

<210> 1701
<211> 255
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic peptide

<400> 1701

Val 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