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(54) Title: ALBUMIN FUSION PROTEINS

(57) Abstract: The present invention encompasses albumin fusion proteins. Nucleic acid molecules encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Additionally the present invention encompasses pharmaceutical compositions comprising albumin fusion proteins and methods of treating, preventing, or ameliorating diseases, disorders or conditions using albumin fusion proteins of the invention.

WO 2009/058322 A1

# Albumin Fusion Proteins

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application is a continuation-in-part application of U.S. Application No. 11/495,624, which claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 60/707,521, filed August 12, 2005; 60/712,386, filed August 31, 2005; 60/732,724, filed November 3, 2005; 60/776,914, filed February 28, 2006; 60/781,361, filed March 13, 2006; 60/810,182, filed June 2, 2006; and 60/813,682, filed June 15, 2006. U.S. Application No. 11/495,624 is also a continuation-in-part of International Application No. PCT/US2005/004041, filed February 9, 2005, which claims benefit under 119(e) of U.S. Provisional Application Nos. 60/542,274, filed February 9, 2004, 60/549,901, filed March 5, 2004, 60/556,906, filed March 29, 2004, and 60/636,603, filed December 17, 2004. U.S. Application No. 11/495,624 is also a continuation-in-part of U.S. Application No. 11/175,690, filed July 7, 2005, which is a continuation of International Application No. PCT/2004/001369, filed January 20, 2004, which claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 60/441,305, filed January 22, 2003; 60/453,201, filed March 11, 2003; 60/467,222, filed May 2, 2003; 60/472,816, filed May 23, 2003; 60/476,267, filed June 6, 2003; 60/505,172, filed September 24, 2003; and 60/506,746, filed September 30, 2003. U.S. Application No. 11/495,624 is also a continuation-in-part of U.S. Application No. 11/429,276, filed May 8, 2006, which is a continuation of U.S. Application No. 10/775,204, filed February 11, 2004, which is a continuation of International Application No. PCT/US2002/40891, filed December 23, 2002, which claims benefit under 35 U.S.C. § 119(e) U.S. Provisional Application Nos. 60/341,811, filed December 21, 2001; 60/350,358, filed January 24, 2002; 60/351,360, filed January 28, 2002; 60/359,370, filed February 26, 2002; 60/360,000, filed February 28, 2002; 60/367,500, filed March 27, 2002; 60/370,227, filed April 8, 2002; 60/378,950, filed May 10, 2002; 60/382,617, filed May 24, 2002; 60/383,123, filed May 28, 2002; 60/385,708, filed June 5, 2002; 60/394,625, filed July 10, 2002; 60/398,008, filed July 24, 2002; 60/402,131, filed August 9, 2002; 60/402,708, filed August 13, 2002; 60/411,426, filed September 18, 2002; 60/411,355, filed September 18, 2002; 60/414,984, filed October 2, 2002; 60/417,611, filed October 11, 2002; 60/420,246, filed October 23, 2002; and 60/423,623, filed November 5, 2002. All of the above listed applications are incorporated by reference herein in their entireties.

## REFERENCE TO SEQUENCE LISTING ON COMPACT DISC

**[0002]** This application refers to a "Sequence Listing," which was provided with U.S. Application No. 11/495,624 as an electronic document on three identical compact discs (CD-R),

labeled "Copy 1," "Copy 2," and "CRF." These compact discs each contain the file "PF617 Sequence Listing.txt" (1,193,482 bytes, created on July 28, 2006), which is incorporated by reference in its entirety.

## BACKGROUND OF THE INVENTION

**[0003]** The invention relates generally to Therapeutic proteins (including, but not limited to, at least one polypeptide, antibody, peptide, or fragment and variant thereof) fused to albumin or fragments or variants of albumin. The invention encompasses polynucleotides encoding therapeutic albumin fusion proteins, therapeutic albumin fusion proteins, compositions, pharmaceutical compositions, formulations and kits. Host cells transformed with the polynucleotides encoding therapeutic albumin fusion proteins are also encompassed by the invention, as are methods of making the albumin fusion proteins of the invention using these polynucleotides, and/or host cells.

**[0004]** Human serum albumin (HSA, or HA), a protein of 585 amino acids in its mature form (as shown in Figure 1 (SEQ ID NO:1)), is responsible for a significant proportion of the osmotic pressure of serum and also functions as a carrier of endogenous and exogenous ligands. At present, HA for clinical use is produced by extraction from human blood. The production of recombinant HA (rHA) in microorganisms has been disclosed in EP 330 451 and EP 361 991.

**[0005]** Therapeutic proteins in their native state or when recombinantly produced, such as interferons and growth hormones, are typically labile molecules exhibiting short shelf-lives, particularly when formulated in aqueous solutions. The instability in these molecules when formulated for administration dictates that many of the molecules must be lyophilized and refrigerated at all times during storage, thereby rendering the molecules difficult to transport and/or store. Storage problems are particularly acute when pharmaceutical formulations must be stored and dispensed outside of the hospital environment.

**[0006]** Few practical solutions to the storage problems of labile protein molecules have been proposed. Accordingly, there is a need for stabilized, long lasting formulations of proteinaceous therapeutic molecules that are easily dispensed, preferably with a simple formulation requiring minimal post-storage manipulation.

**[0007]** Upon *in vivo* administration, therapeutic proteins in their native state or when recombinantly produced, such as interferons and growth hormones, exhibit a short plasma stability due to rapid clearance from the bloodstream. Accordingly, the therapeutic effects provided by these proteins are also short-lived. Thus, in order to sustain their desired therapeutic effect *in vivo*, the rapid clearance of these proteins from the blood dictates that the therapeutic

molecules must be administered more frequently or at a higher dose. However, increasing the dosing schedule for administration of the therapeutic protein often results in an increase in injection site reactions, side-effects, and toxicity in the patient. Similarly, administration of the therapeutic protein at a higher dose also commonly results in an increase in toxicity and side-effects in the patient.

**[0008]** The few practical solutions to increasing plasma stability of therapeutic molecules that have been proposed, including chemical conjugation, have provided limited benefit to the patient. Generally, in most cases, these chemically modified therapeutic molecules are still administered on a frequent dosing schedule, retaining significant injection site reactions, side-effects, and toxicity in patients. Accordingly, there is a need for an stabilized form of therapeutic molecules that retains a higher plasma stability in vivo than the native or recombinantly produced therapeutic alone and can be administered less frequently, thereby decreasing potential side-effects to the patient.

## SUMMARY OF THE INVENTION

**[0009]** The present invention encompasses albumin fusion proteins comprising a Therapeutic protein (e.g., a polypeptide, antibody, or peptide, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin. The present invention also encompasses polynucleotides comprising, or alternatively consisting of, nucleic acid molecules encoding a Therapeutic protein (e.g., a polypeptide, antibody, or peptide, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin. The present invention also encompasses polynucleotides, comprising, or alternatively consisting of, nucleic acid molecules encoding proteins comprising a Therapeutic protein (e.g., a polypeptide, antibody, or peptide, or fragment or variant thereof) fused to albumin or a fragment (portion) or variant of albumin, that is sufficient to prolong the shelf life of the Therapeutic protein, to increase the plasma stability of the Therapeutic protein compared to its unfused state, and/or stabilize the Therapeutic protein and/or its activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo*. Albumin fusion proteins encoded by a polynucleotide of the invention are also encompassed by the invention, as are host cells transformed with polynucleotides of the invention, and methods of making the albumin fusion proteins of the invention and using these polynucleotides of the invention, and/or host cells.

**[0010]** In a preferred aspect of the invention, albumin fusion proteins include, but are not limited to, those described in Table 2 and the polynucleotides encoding such proteins.

**[0011]** The invention also encompasses pharmaceutical formulations comprising an albumin

fusion protein of the invention and a pharmaceutically acceptable diluent or carrier. Such formulations may be in a kit or container. Such kit or container may be packaged with instructions pertaining to the extended shelf life of the Therapeutic protein. Such formulations may be used in methods of treating, preventing, ameliorating or diagnosing a disease or disease symptom in a patient, preferably a mammal, most preferably a human, comprising the step of administering the pharmaceutical formulation to the patient.

**[0012]** In other embodiments, the present invention encompasses methods of preventing, treating, or ameliorating a disease or disorder. In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indication: Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired an albumin fusion protein of the invention that comprises a Therapeutic protein or portion corresponding to a Therapeutic protein (or fragment or variant thereof) disclosed in the "Therapeutic Protein: X" column of Table 1 (in the same row as the disease or disorder to be treated as listed in the "Preferred Indication: Y" column of Table 1) in an amount effective to treat, prevent or ameliorate the disease or disorder.

**[0013]** In one embodiment, an albumin fusion protein described in Table 1 or 2 has extended shelf life.

**[0014]** In a second embodiment, an albumin fusion protein described in Table 1 or 2 is more stable than the corresponding unfused Therapeutic molecule described in Table 1.

**[0015]** The present invention further includes transgenic organisms modified to contain the nucleic acid molecules of the invention (including, but not limited to, the polynucleotides described in Tables 1 and 2), preferably modified to express an albumin fusion protein of the invention.

## BRIEF DESCRIPTION OF THE FIGURES

**[0016]** Figure 1A-D shows the amino acid sequence of the mature form of human albumin (SEQ ID NO:1) and a polynucleotide encoding it (SEQ ID NO:2). Nucleotides 1 to 1755 of SEQ ID NO:2 encode the mature form of human albumin (SEQ ID NO:1).

**[0017]** Figure 2 shows the restriction map of the pPPC0005 cloning vector ATCC deposit PTA-3278.

**[0018]** Figure 3 shows the restriction map of the pSAC35 yeast *S. cerevisiae* expression vector (Sleep *et al.*, BioTechnology 8:42 (1990)).

**[0019]** Figure 4 compares the anti-proliferative activity of IFN albumin fusion protein encoded by CID 3165 (CID 3165 protein) and recombinant IFNa (rIFNa) on Hs294T melanoma cells. The

cells were cultured with varying concentrations of either CID 3165 protein or rIFNa and proliferation was measured by BrdU incorporation after 3 days of culture. CID 3165 protein caused measurable inhibition of cell proliferation at concentrations above 10 ng/ml with 50% inhibition achieved at approximately 200 ng/ml. (■) = CID 3165 protein, (◆) = rIFNa.

**[0020]** Figure 5 shows the effect of various dilutions of IFNa albumin fusion proteins on SEAP activity in the ISRE-SEAP/293F reporter cells. One preparation of IFNa fused upstream of albumin (◆) was tested, as well as two different preparations of IFNa fused downstream of albumin (●) and (■).

**[0021]** Figure 6 shows the effect of time and dose of IFNa albumin fusion protein encoded by DNA comprised in construct 2249 (CID 2249 protein) on the mRNA level of OAS (p41) in treated monkeys (see Example 76). Per time point: first bar = Vehicle control, 2nd bar = 30 ug/kg CID 2249 protein day 1 iv, third bar = 30 ug/kg CID 2249 protein day 1 sc, 4th bar = 300 ug/kg CID 2249 protein day 1 sc, 5th bar = 40 ug/kg recombinant IFNa day 1, 3 and 5 sc.

**[0022]** Figure 7 shows the dose-response relationship of BNP albumin fusion proteins encoded by DNA comprised in constructs CID 3691 and 3618 (CID 3691 and 3618 protein) on activating cGMP formation in NPR-A/293F reporter cells (see Examples 78 and 79). Both BNP peptide (■), as well as, two different preparations of BNP fused upstream of albumin (□) and (●) were tested.

**[0023]** Figure 8 shows the effect of BNP albumin fusion protein on mean arterial pressure in spontaneously hypertensive rats (see Example 78). Vehicle (□), BNP peptide (●), or BNP albumin fusion protein (○) were delivered via tail vein injection. Systolic and diastolic blood pressures were recorded by cuff-tail method.

**[0024]** Figure 9 shows the plasma cGMP levels in eleven- to 12-week-old male C57/BL6 mice after intravenous injection of recombinant BNP peptide (●) or BNP albumin fusion protein (○ (see Example 78). cGMP levels were determined from plasma prepared from tail bleeds collected at several time points after intravenous injection.

**[0025]** Figure 10 shows the dose-response relationship of BNP peptide and BNP albumin fusion proteins encoded by DNA comprised in constructs CID 3796 and 3959 on activating cGMP formation in NPR-A/293F reporter cells (see Example 80). Both BNP peptide (■), as well as, two different preparations comprising BNP fused downstream of albumin, (□) and (◇) were tested.

**[0026]** Figure 11A shows the dose-response relationship of BNP and ANP peptides with or without treatment of neprilysin for 24 hours on activating cGMP formation in NPR-A/293F

reporter cells (see Example 81).

**[0027]** Figure 11B shows the dose-reponse relationship of ANP peptide on activating cGMP formation in NPR-A/293F reporter cells following treatment of neprilysin or control MES buffer for 20 minutes, 1 hour, or 24 hours (see Example 81).

**[0028]** Figure 11C shows the dose-reponse relationship of ANP albumin fusion protein comprising ANP fused upstream of albumin and encoded by DNA comprised in construct CID3484 on activating cGMP formation in NPR-A/293F reporter cells following treatment of neprilysin or control MES buffer for 20 minutes, 1 hour, or 24 hours (see Example 81).

**[0029]** Figure 11D shows the percentage of intact natriuretic peptides following treatment with neprilysin for the specified time. Both ANP and BNP peptides, as well as, two albumin fusion proteins comprising BNP fused upstream of albumin via tripartite glycines (CID 3809) and ANP fused upstream to albumin (CID 3484) were tested (see Example 81).

**[0030]** Figure 12 shows the reduction in HCV RNA titer, as measured by median HCV RNA change ($log_{10}$ IU/ml), in patients infected with chronic hepatitis C genotype 1 and who have previously failed to respond to at least one treatment regimen of pegylated interferon alpha in combination with ribavirin (PEG-RBV) (nonresponders) following treatment with HSA-IFNα2b in combination with ribavirin for 0 to 24 weeks.

**[0031]** Figures 13A and B show the effect of HSA-BNP (Construct ID #3959) on plasma and urine cGMP levels, respectively following administration of an 5 mg/kg IV bolus in normal healthy pigs (n = 4-6/group). Asterisks indicate significant differences in cGMP levels from vehicle ($p<0.05$).

**[0032]** Figure 14A shows the effect of administration of an intravenous bolus of 2 mg/kg or 6 mg/kg HSA-BNP (Construct ID #3959) on end-diastolic diameter change in a porcine experimental heart failure model (n = 10/group). Heart failure was induced in the pig by ventricular pacing. End diastolic diameter was measure by echocardiography. Significant changes ($p<0.05$) from vehicle or baseline are indicated (& and #, respectively).

**[0033]** Figure 14B shows the effect of administration of an intravenous bolus of 2 mg/kg or 6 mg/kg HSA-BNP (Construct ID #3959) on fractional shortening in a porcine experimental heart failure model (n = 10/group). Heart failure was induced in the pig by ventricular pacing. Significant changes ($p<0.05$) from vehicle or baseline are indicated (& and #, respectively).

**[0034]** Figures 15A-H show the hemodynamic effects of HSA-BNP (Construct ID #3959) administered via a single intravenous bolus at 0.5 mg/kg or 5 mg/kg in a normal dog model. Cardiac output (CO), mean arterial pressure (MAP), pulmonary capillary wedge pressure

(PCWP) and pulmonary arterial pressure (PAP) were measured at baseline prior to intravenous bolus of 0.5 mg/kg or 5 mg/kg HSA-BNP (Construct ID #3959) and at 30, 60, 90, 150, 210, and 270 post-infusion in anesthesized normal mongrels (n = 8/group). Asterisks indicate statistically significant changes from baseline ($p<0.05$).

**[0035]** Figures 16A-H show the renal effects of HSA-BNP (Construct ID #3959) administered via a single intravenous bolus at 0.5 mg/kg or 5 mg/kg in a normal dog model. Urine flow (rate/30 minute collection), sodium excretion, renal blood flow, and glomerular filtration rate (GFR) were measured at baseline prior to intravenous bolus of 0.5 mg/kg or 5 mg/kg HSA-BNP (Construct ID #3959) and at 30, 60, 90, 150, 210, and 270 post-infusion in anesthesized normal mongrels (n = 8/group). Asterisks indicate statistically significant changes from baseline ($p<0.05$).

**[0036]** Figures 17A-F show the hormonal effects of HSA-BNP (Construct ID #3959) administered via a single intravenous bolus at 0.5 mg/kg or 5 mg/kg in a normal dog model. Plasma aldosterone, renin, and angiotensin II levels were measured at baseline prior to intravenous bolus of 0.5 mg/kg or 5 mg/kg HSA-BNP (Construct ID #3959) and at 30, 60, 90, 150, 210, and 270 post-infusion in anesthesized normal mongrels (n = 8/group). Asterisks indicate statistically significant changes from baseline ($p<0.05$).

**[0037]** Figures 18A-C show the effect of a single intravenous bolus of 5 mg/kg HSA-BNP (Construct ID #3959) on systolic and mean arterial blood pressure in normal, healthy, awake beagles surgically implanted with a Data Sciences International radiotelemetry transmitter, which had systemic arterial blood pressure, heart rate and ECG data collection capabilities. Change from baseline of systolic blood pressure (Figure 18A), difference in mean systolic blood pressure (Figure 18B), and change from baseline in mean arterial pressures (Figure 18C) over 48 hours of continuous data recording following infusion are presented. Asterisks indicate a statistically significant difference in baseline-adjusted mean values for 5 mg/kg HSA-BNP (Construct ID #3959) compared to vehicle ($p<0.05$).

**[0038]** Figures 19A and B show a comparison of the effect of an intravenous bolus of 0.02 mg/kg unfused BNP peptide and a subcutaneous injection of 10 mg/kg HSA-BNP (Construct ID #3959) on systemic blood pressure in normal, healthy, awake beagles surgically implanted with a Data Sciences International radiotelemetry transmitter, which had systemic arterial blood pressure, heart rate and ECG data collection capabilities. Change from baseline of systolic blood pressure over 48 hours of continuous data recording following administration of BNP (Figure 19A) and HSA-BNP (Construct ID #3959) are presented. Asterisks indicate a statistically significant

difference in baseline-adjusted mean values for 5 mg/kg HSA-BNP (Construct ID #3959) compared to vehicle ($p<0.05$).

**[0039]** Figure 20 shows the nucleic acid sequence and amino acid sequence of a BChE-albumin fusion. The fusion is discussed in Example 90.

**[0040]** Figure 21. Catalytic power of wild-type BChE (WT) and cocaine hydrolases derived from this enzyme. Values are expressed as kcat (molecules of natural, (-)-cocaine hydrolyzed per min per molecule of enzyme). Amino acid substitutions in the BChE mutants are: A328W/Y332A (CocE, Sun et al., 2002); F227A/S287G /A328W/Y332A (AME359, Pancook et al 2003); A328W/Y332G/S287G/A199S (CocH, Pan et al, 2004).

**[0041]** Figure 22. Purification and titration of Albu-CocH. A) Coomassie-Blue stained SDS electrophoresis gel of final product (M = markers, R = sample under reducing conditions, NR = sample under non-reducing conditions). B) Assessment of purify by size-exclusion chromatography (SEC-HPLC) and N-terminal sequencing. C) Active site titration. Residual BChE activity was reduced in linear fashion after overnight incubation with increasing sub-stoichiometric amounts of the irreversible organophosphate cholinesterase inhibitor, di-isopropylfluorophosphate (DFP). The X-axis intercept with this typical batch (one of three) indicates approximately 7.7 pmol of active site serine residues (the putative DFP target). The amount of enzyme protein was 0.72 µg, equivalent to 8.5 pmol. Thus, over 90% of the purified material was enzymatically active.

**[0042]** Figure 23. Stability of Albu-CocH in vivo. Representative time course of plasma cocaine hydrolase activity in 1 of 5 rats injected at zero-time with Albu-CocH, 3 mg/kg i.v. These data, fitted to a double exponential decay equation, indicated a terminal elimination half-life of 7.9 hr. The higher slope at early times suggests a preliminary redistribution phase, which might represent enzyme binding to tissue components, metabolic destruction, or limited transcapillary passage into extracellular fluid.

**[0043]** Figure 24. Blunting of cocaine-induced hypertension. Rats were anesthetized with urethane (1.45 g/kg) for arterial cannulation. Subsequently Albu-CocH was administered (filled circles, 3 mg/kg, i.v.) or saline (open circles), followed by atropine (1 mg/kg) to reduce vagal reflexes, and baseline pressure was recorded for 10 min. At zero time, the rats were challenged with cocaine (3.5 mg/kg) and at 10 min with norepinephrine (NE, 6 µg/kg). Changes in mean blood pressure are shown (mean ± SEM, 5 rats per group).

**[0044]** Figure 25. Prevention and rescue from cocaine overdose. A: Percent incidence of arousal and seizures when cocaine (100 mg/kg i.p.) was given 10 min after i.v. saline (n = 10),

Albu-CocH (n = 6 per dose), or wild type BChE (WT, n = 3). B: effect of Albu-CocH (10 mg/kg) on the dose-response curve for seizures from cocaine administered 10 min later (n = 6 per group).

**[0045]** Figure 26. Accelerated cocaine clearance. Plasma cocaine levels are shown as a function of time after injection of cocaine (30 μCi, 3.5 mg/kg, i.v.) into rats that 10 min earlier had received Albu-CocH (3 mg/kg i.v--filled symbols, n = 4) or saline (empty symbols, n = 4). Blood samples were drawn from the femoral artery beginning 30 seconds (sec) after cocaine and were assayed radiometrically. As shown here, plasma cocaine levels in control rats declined slowly but in Albu-CocH-treated rats they dropped nearly to the detection limit by the earliest sampling point (30 sec after drug injection).

**[0046]** Figure 27. Reduced tissue accumulation of cocaine. Rats (n = 4 per group) received 3H-cocaine (30 μCi, 3.5 mg/kg, i.v.) 10 min after treatment with Albu-CocH (3 mg/kg, i.v.) or saline. Ten min after the cocaine injections, brains, hearts, and plasma were collected for analysis of cocaine and its metabolite, benzoic acid. Treatment with Albu-CocH greatly lowered tissue burden. Intact cocaine was nearly undetectable in hearts and plasma from the enzyme-treated rats, where it was quantitatively replaced by the metabolite, benzoic acid. The treatment effect was substantial in brain as well, but smaller, consistent with the fact that nervous tissue is a preferred site for cocaine uptake.

**[0047]** Figure 28. Selective block of cocaine-primed reinstatement of drug-seeking behavior. Fifteen rats that had previously self-administered cocaine and extinguished when cocaine was replaced with saline were primed with an i.v. injection of saline (S), cocaine (C, 10 mg/kg) or amphetamine (A, 2 mg/kg) just before each of twelve daily, 2-hr sessions. On days 4 and 6, they received Albu-CocH enzyme (E), 2 mg/kg i.v., 2 hr beforehand. Data shown are mean ± SEM of total responses on the previously active lever (which had no consequences). Horizontal brackets indicate statistical comparisons (* $p < 0.05$; ** $p < 0.01$).

## DETAILED DESCRIPTION

### Definitions

**[0048]** The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

**[0049]** As used herein, "polynucleotide" refers to a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one Therapeutic

protein X (or fragment or variant thereof); a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NO:Y (as described in column 6 of Table 2) or a fragment or variant thereof; a nucleic acid molecule having a nucleotide sequence comprising or alternatively consisting of the sequence shown in SEQ ID NO:X; a nucleic acid molecule having a nucleotide sequence encoding a fusion protein comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NO:Z; a nucleic acid molecule having a nucleotide sequence encoding an albumin fusion protein of the invention generated as described in Table 2 or in the Examples; a nucleic acid molecule having a nucleotide sequence encoding a Therapeutic albumin fusion protein of the invention, a nucleic acid molecule having a nucleotide sequence contained in an albumin fusion construct described in Table 2, or a nucleic acid molecule having a nucleotide sequence contained in an albumin fusion construct deposited with the ATCC (as described in Table 3).

**[0050]** As used herein, "albumin fusion construct" refers to a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof); a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof) generated as described in Table 2 or in the Examples; or a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof), further comprising, for example, one or more of the following elements: (1) a functional self-replicating vector (including but not limited to, a shuttle vector, an expression vector, an integration vector, and/or a replication system), (2) a region for initiation of transcription (e.g., a promoter region, such as for example, a regulatable or inducible promoter, a constitutive promoter), (3) a region for termination of transcription, (4) a leader sequence, and (5) a selectable marker. The polynucleotide encoding the Therapeutic protein and albumin protein, once part of the albumin fusion construct, may each be referred to as a "portion," "region" or "moiety" of the albumin fusion construct.

**[0051]** The present invention relates generally to polynucleotides encoding albumin fusion proteins; albumin fusion proteins; and methods of treating, preventing, or ameliorating diseases or disorders using albumin fusion proteins or polynucleotides encoding albumin fusion proteins.

As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). An albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another by genetic fusion (i.e., the albumin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a Therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of albumin). The Therapeutic protein and albumin protein, once part of the albumin fusion protein, may each be referred to as a "portion", "region" or "moiety" of the albumin fusion protein (e.g., a "Therapeutic protein portion" or an "albumin protein portion"). In a highly preferred embodiment, an albumin fusion protein of the invention comprises at least one molecule of a Therapeutic protein X or fragment or variant of thereof (including, but not limited to a mature form of the Therapeutic protein X) and at least one molecule of albumin or fragment or variant thereof (including but not limited to a mature form of albumin).

**[0052]** In a further preferred embodiment, an albumin fusion protein of the invention is processed by a host cell and secreted into the surrounding culture medium. Processing of the nascent albumin fusion protein that occurs in the secretory pathways of the host used for expression may include, but is not limited to signal peptide cleavage; formation of disulfide bonds; proper folding; addition and processing of carbohydrates (such as for example, N- and O- linked glycosylation); specific proteolytic cleavages; and assembly into multimeric proteins. An albumin fusion protein of the invention is preferably in the processed form. In a most preferred embodiment, the "processed form of an albumin fusion protein" refers to an albumin fusion protein product which has undergone N- terminal signal peptide cleavage, herein also referred to as a "mature albumin fusion protein".

**[0053]** In several instances, a representative clone containing an albumin fusion construct of the invention was deposited with the American Type Culture Collection (herein referred to as "ATCC®"). Furthermore, it is possible to retrieve a given albumin fusion construct from the deposit by techniques known in the art and described elsewhere herein. The ATCC® is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC® deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

**[0054]** In one embodiment, the invention provides a polynucleotide encoding an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin

protein. In a further embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein. In a preferred embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a serum albumin protein encoded by a polynucleotide described in Table 2. In a further preferred embodiment, the invention provides a polynucleotide encoding an albumin fusion protein whose sequence is shown as SEQ ID NO:Y in Table 2. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a Therapeutic protein and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a Therapeutic protein and a serum albumin protein. In preferred embodiments, the serum albumin protein component of the albumin fusion protein is the mature portion of serum albumin. The invention further encompasses polynucleotides encoding these albumin fusion proteins.

**[0055]** In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein, and a biologically active and/or therapeutically active fragment of serum albumin. In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a biologically active and/or therapeutically active variant of serum albumin. In preferred embodiments, the Therapeutic protein portion of the albumin fusion protein is the mature portion of the Therapeutic protein. In a further preferred embodiment, the Therapeutic protein portion of the albumin fusion protein is the extracellular soluble domain of the Therapeutic protein. In an alternative embodiment, the Therapeutic protein portion of the albumin fusion protein is the active form of the Therapeutic protein. The invention further encompasses polynucleotides encoding these albumin fusion proteins.

**[0056]** In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment or variant of a Therapeutic protein and a biologically active and/or therapeutically active fragment or variant of serum albumin. In preferred embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, the mature portion of a Therapeutic protein and the mature portion of serum albumin. The invention further encompasses polynucleotides encoding these albumin fusion proteins.

**Therapeutic proteins**

**[0057]** As stated above, a polynucleotide of the invention encodes a protein comprising or alternatively consisting of, at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion.

**[0058]** An additional embodiment includes a polynucleotide encoding a protein comprising or alternatively consisting of at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are linked with one another by chemical conjugation.

**[0059]** As used herein, "Therapeutic protein" refers to proteins, polypeptides, antibodies, peptides or fragments or variants thereof, having one or more therapeutic and/or biological activities. Therapeutic proteins encompassed by the invention include but are not limited to, proteins, polypeptides, peptides, antibodies, and biologics. (The terms peptides, proteins, and polypeptides are used interchangeably herein.) It is specifically contemplated that the term "Therapeutic protein" encompasses antibodies and fragments and variants thereof. Thus a protein of the invention may contain at least a fragment or variant of a Therapeutic protein, and/or at least a fragment or variant of an antibody. Additionally, the term "Therapeutic protein" may refer to the endogenous or naturally occurring correlate of a Therapeutic protein.

**[0060]** By a polypeptide displaying a "therapeutic activity" or a protein that is "therapeutically active" is meant a polypeptide that possesses one or more known biological and/or therapeutic activities associated with a therapeutic protein such as one or more of the Therapeutic proteins described herein or otherwise known in the art. As a non-limiting example, a "Therapeutic protein" is a protein that is useful to treat, prevent or ameliorate a disease, condition or disorder. As a non-limiting example, a "Therapeutic protein" may be one that binds specifically to a particular cell type (normal (e.g., lymphocytes) or abnormal e.g., (cancer cells)) and therefore may be used to target a compound (drug, or cytotoxic agent) to that cell type specifically.

**[0061]** For example, a non-exhaustive list of "Therapeutic protein" portions which may be comprised by an albumin fusion protein of the invention includes, but is not limited to, IFNα, , ANP, BNP, LANP, VDP, KUP, CNP, DNP, HCC-1, beta defensin-2, fractalkine, oxyntomodulin, killer toxin peptide, TIMP-4, PYY, adrenomedullin, ghrelin, CGRP, IGF-1, neuraminidase, hemagglutinin, butyrylcholinesterase, endothelin, and mechano growth factor.

**[0062]** Interferon hybrids may also be fused to the amino or carboxy terminus of albumin to form an interferon hybrid albumin fusion protein. Interferon hybrid albumin fusion protein may have enhanced, or alternatively, suppressed interferon activity, such as antiviral responses, regulation

of cell growth, and modulation of immune response (Lebleu et al., *PNAS* USA, 73:3107-3111 (1976); Gresser et al., *Nature*, 251:543-545 (1974); and Johnson, *Texas Reports Biol Med*, 35:357-369 (1977)). Each interferon hybrid albumin fusion protein can be used to treat, prevent, or ameliorate viral infections (*e.g.*, hepatitis (*e.g.*, HCV); or HIV), multiple sclerosis, or cancer.

**[0063]** In one embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon alpha-interferon alpha hybrid (herein referred to as an alpha-alpha hybrid). For example, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha D. In a further embodiment, the A/D hybrid is fused at the common BglII restriction site to interferon alpha D, wherein the N-terminal portion of the A/D hybrid corresponds to amino acids 1-62 of interferon alpha A and the C-terminal portion corresponds to amino acids 64-166 of interferon alpha D. For example, this A/D hybrid would comprise the amino acid sequence: CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI QQIFNLFTTKDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNX$_2$DSILAV KKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO:99), wherein the $X_1$ is R or K and the $X_2$ is A or V. In an additional embodiment, the A/D hybrid is fused at the common PvuIII restriction site, wherein the N-terminal portion of the A/D hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha D. For example, this A/D hybrid would comprise the amino acid sequence: CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI QQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVMQEERVGETPLMNX$_2$DSILAV KKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO:100), wherein the $X_1$ is R or K and the second $X_2$ is A or V. These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety.

**[0064]** In an additional embodiment, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha F. In a further embodiment, the A/F hybrid is fused at the common PvuIII restriction site, wherein the N-terminal portion of the A/F hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha F. For example, this A/F hybrid would comprise the amino acid sequence: CDLPQTHSLGSRRTLMLLAQMRXISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMIQ QIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDMEACVIQEVGVEETPLMNVDSILAVK

KYFQRITLYLTEKKYSPCAWEVVRAEIMRSFSLSKIFQERLRRKE (SEQ ID NO:101), wherein X is either R or K. These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety. In a further embodiment, the alpha-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha A fused to interferon alpha B. In an additional embodiment, the A/B hybrid is fused at the common PvuIII restriction site, wherein the N-terminal portion of the A/B hybrid corresponds to amino acids 1-91 of interferon alpha A and the C-terminal portion corresponds to amino acids 93-166 of interferon alpha B. For example, this A/B hybrid would comprise an amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRX$_1$ISLFSCLKDRHDFGFPQEEFGNQFQKAETIPVLHEMI QQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEX$_2$X$_3$X$_4$X$_5$QEVGVIESPLMYEDSILA VRKYFQRITLYLTEKKYSSCAWEVVRAEIMRSFSLSINLQKRLKSKE (SEQ ID NO:102), wherein the $X_1$ is R or K and $X_2$ through $X_5$ is SCVM or VLCD. These hybrids are further described in U.S. Patent No. 4,414,510, which is hereby incorporated by reference in its entirety.

**[0065]** In another embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon beta-interferon alpha hybrid (herein referred to as a beta-alpha hybrid). For example, the beta-alpha hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon beta-1 fused to interferon alpha D (also referred to as interferon alpha-1). In a further embodiment, the beta-1/alpha D hybrid is fused wherein the N-terminal portion corresponds to amino acids 1-73 of interferon beta-1 and the C-terminal portion corresponds to amino acids 74-167 of interferon alpha D. For example, this beta-1/alpha D hybrid would comprise an amino acid sequence:

MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIY EMLQNIFAIFRQDSSAAWDEDLLDKFCTELYQQLNDLEACVMQEERVGETPLMNXDSIL AVKKYFRRITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNLQERLRRKE (SEQ ID NO:103), wherein X is A or V. These hybrids are further described in U.S. Patent No. 4,758,428, which is hereby incorporated by reference in its entirety.

**[0066]** In another embodiment, the interferon hybrid portion of the interferon hybrid albumin fusion protein comprises an interferon alpha-interferon beta hybrid (herein referred to as a alpha-beta hybrid). For example, the alpha-beta hybrid portion of the interferon hybrid albumin fusion protein consists, or alternatively comprises, of interferon alpha D (also referred to as interferon alpha-1) fused to interferon beta-1. In a further embodiment, the alpha D/beta-1 hybrid is fused wherein the N-terminal portion corresponds to amino acids 1-73 of interferon alpha D and the C-

terminal portion corresponds to amino acids 74-166 of interferon beta-1. For example, this alpha D/beta-1 hybrid would have an amino acid sequence:

MCDLPETHSLDNRRTLMLLAQMSRISPSSCLMDRHDFGFPQEEFDGNQFQKAPAISVLHE LIQQIFNLFTTKDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSLH LKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN (SEQ ID NO:104).

These hybrids are further described in U.S. Patent No. 4,758,428, which is hereby incorporated by reference in its entirety.

**[0067]** In further embodiments, the interferon hybrid portion of the interferon hybrid albumin fusion proteins may comprise additional combinations of alpha-alpha interferon hybrids, alpha-beta interferon hybrids, and beta-alpha interferon hybrids. In additional embodiments, the interferon hybrid portion of the interferon hybrid albumin fusion protein may be modified to include mutations, substitutions, deletions, or additions to the amino acid sequence of the interferon hybrid. Such modifications to the interferon hybrid albumin fusion proteins may be made, for example, to improve levels of production, increase stability, increase or decrease activity, or confer new biological properties.

**[0068]** The above-described interferon hybrid albumin fusion proteins are encompassed by the invention, as are host cells and vectors containing polynucleotides encoding the polypeptides. In one embodiment, a interferon hybrid albumin fusion protein encoded by a polynucleotide as described above has extended shelf life. In an additional embodiment, a interferon hybrid albumin fusion protein encoded by a polynucleotide described above has a longer serum half-life and/or more stabilized activity in solution (or in a pharmaceutical composition) *in vitro* and/or *in vivo* than the corresponding unfused interferon hybrid molecule.

**[0069]** In another non-limiting example, a "Therapeutic protein" is a protein that has a biological activity, and in particular, a biological activity that is useful for treating, preventing or ameliorating a disease. A non-inclusive list of biological activities that may be possessed by a Therapeutic protein includes, inhibition of HIV-1 infection of cells, stimulation of intestinal epithelial cell proliferation, reducing intestinal epithelial cell permeability, stimulating insulin secretion, induction of bronchodilation and vasodilation, inhibition of aldosterone and renin secretion, blood pressure regulation, promoting neuronal growth, enhancing an immune response, enhancing inflammation, suppression of appetite, or any one or more of the biological activities described in the "Biological Activities" section below and/or as disclosed for a given Therapeutic protein in Table 1 (column 2).

**[0070]** In one embodiment, IFN-alpha-HSA fusions are used to inhibit viral agents classified

under Category A- Filo (Ebola), Arena (Pichende), Category B- Toga (VEE) or Category C- Bunya (Punto toro), Flavi (Yellow fever, West Nile). For example, CPE inhibition, neutral red staining and virus yield assays were employed to evaluate the antiviral activities of INF-alpha fused downstream of HSA (CID 3165 protein). The pharmacokinetics and pharmacodynamic activity of CID 3165 protein in cynomolgus monkeys and human subjects were evaluated. The results indicate that antiviral activity was achieved against all the RNA viruses evaluated with a favorable safety index. The IC50 values ranged from <0.1 ng/ml (Punta Toro A) to 19 ng/ml (VEE) in the CPE assay. In cynomolgus monkeys, the half-life of CID 3165 protein was 90 hours and was detectable up to 14 days post-dose. In human subjects, CID 3165 protein was safe and well tolerated. $C_{max}$ following single injection doses was dose-proportional. The mean $C_{max}$ in the 500 ug cohort was 22 ng/ml, and the mean $t_{1/2}$ was 150 hours. Dosing once every 2-4 weeks or more is supported by the pharmacokinetics. Antiviral response against Hepatitis C was observed in the majority of subjects in the single injection cohorts (120-500 ug).

**[0071]** In a further embodiment, IFN-alpha-HSA fusions are used to treat patients with chronic Hepatitis C infection (HCV). Interferon alpha, also known as interferon alfa or leukocyte interferon, is the standard of care for treatment of patients infected with HCV. The term "interferon alpha" refers to a family of highly homologous related polypeptides with anti-viral activity. The interferon alpha portion of the IFN-alpha-HSA fusion consists or alternatively comprises any interferon alpha or fragment thereof known in the art. Non-limiting examples of the interferon alpha portion of the IFN-alpha-HSA fusion proteins of the invention include, but are not limited to, the interferon alpha proteins disclosed in the Therapeutic protein column of Table 1. In particular embodiments, the interferon alpha portion consists or alternatively comprises interferon alpha-2a, interferon alpha-2b, interferon alpha-2c, consensus interferon, interferon alfacon-1, interferon alpha-n1, interferon alpha-n3, any commercially available form of interferon alpha, such as, for example, INTRON® A (Schering Corp., Kenilworth, N.J.), ROFERON® A (Hoffman-La Roche, Nutley, N.J.), Berofor alpha inteferon (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefied, Conn.), OMNIFERON™ (Viragen, Inc., Plantation, FL), MULTIFERON™ (Viragen, Inc., Plantation, FL) WELLFERON® (GlaxoSmithKline, London, Great Britian), INFERGEN® (Amgen, Inc., Thousands Oaks, CA), SUMIFERON® (Sumitomo, Japan), BELEROFON® (Nautilus Biotech, France), MAXY-ALPHA™ (Maxygen, Redwood City, CA / Hoffman-La Roche, Nutley, N.J.), or any purified interferon alpha product or a fragment thereof. In further embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein consists or alternatively comprises interferon alpha modified or formulated

for extended or controlled release. For example, the interferon alpha portion consists, or alternatively comprises commercially available extended release or controlled release interferon alpha, including, but not limited to interferon-alpha-XL (Flamel Technologies, France) and LOCTERON™ (BioLex Therapeutics/OctoPlus, Pittsboro, NC). In additional embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein may be modified by the attachment of chemical moieties. For example, the inteferon alpha portion may be modified by pegylation. Accordingly, in additional embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein consists or alternatively comprises pegylated forms of interferon alpha-2a, 2b, or consensus interferon and include, but are not limited to, a commercially available pegylated interferon alpha, such as, for example, PEG-INTRON® (Schering Corp., Kenilworth, N.J.), PEGASYS® (Hoffman-La Roche, Nutley, N.J.), PEG-OMNIFERON™ (Viragen, Inc., Plantation, FL) or a fragment thereof. However, as used herein, "IFN-alpha-HSA" fusions refers to the HSA fused to any of the interferon alpha proteins known in the art or a fragment thereof.

**[0072]** Patients infected with HCV may fall within two categories based on previous exposure to an interferon regimen for treatment of the HCV infection. "Treatment-naive patients" or "naïve patients" are those patients who have never been treated with an interferon regimen. "Treatment-experienced patients" or "experienced patients" are those patients who have been treated or are currently being treated with an interferon regimen. "Non-responders" are experienced patients who have been previously treated with an interferon regimen but have failed to meet the primary endpoint of treatment such as an early viral load reduction (EVR) or an end-of-treatment response (ETR). "Relapsers" are experienced patients who have previously been treated with an interferon regimen and have a achieved primary endpoint of treatment such as EVR or ETR, but become subsequently positive for HCV at later time points. However, as used herein, an "HCV patient" refers to a patient who is infected with HCV and who is either naïve or experienced. In addition, as used herein, an "HCV patient" who is "experienced" is either a non-responder or a relapser.

**[0073]** In addition, the Hepatitis C virus can be classified into numerous genotypes, with four genotypes, genotype 1, 2, 3, or 4, being the most prevalent. Generally, the Hepatitis C virus that infects an HCV patient comprises a single genotype. However, the Hepatitis virus can comprise a combination of two or more genotypes. In addition, the genotype of Hepatitis C virus may also be a variant of one of the known HCV genotypes. In a further embodiment, the Hepatitis C virus of the HCV patient is genotype 1 or a variant thereof. However, as used herein, "HCV" refers to the Hepatitis C virus of any genotype, or combination or variants thereof.

**[0074]** The standard treatment regimen for patients with HCV involves treatment with interferon

alpha in combination with an antiviral agent, such as, ribavirin. In general, the interferon alpha is administered daily, twice-a-week, or weekly and the ribavirin is administered daily. However, recent studies have also used inteferon alpha in combination with other antiviral agents known in the art for the treatment of HCV. Thus, in a further embodiment the IFN-alpha-HSA fusion may be administered to the HCV patient either alone or in combination with an antiviral agent, such as, for example, ribavirin. In a more preferred embodiment, IFN-alpha-HSA fusion may be administered to the HCV patient in combination with one, two three, or more antiviral agents, such as, for example, ribavirin and an additional antiviral agent.

**[0075]** As noted above, pharmokinetics of the CID 3165 protein support a dosing schedule of once every 2-4 weeks or greater. Thus, in a further embodiment, the HCV patients are treated with an IFN-alpha-HSA fusion by administration once every 2-4 weeks alone or in combination with an effective amount of an antiviral agent. In a preferred embodiment, the HCV patients are treated with an IFN-alpha-HSA fusion by administration once every 2-4 weeks in combination with an effective amount of one, two three, or more antiviral agents. In an additional preferred embodiment, the IFN-alpha-HSA fusion is administered to the HCV patient once every 4 weeks. In an additional preferred embodiment, the IFN-alpha-HSA fusion is administered to the HCV patient more than once every 4 weeks. In additional embodiments, the IFN-alpha-HSA fusion is adminstered once every 4 weeks or more to an HCV patient, wherein the treatment also includes administration of an effective amount of one, two three, or more antiviral agents.

**[0076]** In a another embodiment, IFN-alpha-HSA fusions may be used as a low-dose monotherapy for maintenance therapy of HCV. In a further additional embodiment, IFN-alpha-HSA fusions may used in combination with ribavirin and one or more other antiviral agents for the treatement of HCV. Alternatively, in another embodiment, IFN-alpha-HSA fusions may be used in combination with one, two, three, or more antiviral agents, other than ribavirin, for the treatment of HCV.

**[0077]** In an additional embodiment, IFN-alpha-HSA fusions may be used for the treatment of other viral infections. For example, in one embodiment, IFN-alpha-HSA fusions may be used for the treatment of Hepatitis B (HBV). In an additional embodiment, IFN-alpha-HSA fusions may be used for the treatment of Human Papilloma Virus (HPV). In a further embodiment, IFN-alpha-HSA fusions may be used in the treatment of cancer, including, but not limited to hairy cell leukemia, malignant melanoma, follicular lymphoma, chronic myelogenous leukemia, AIDS related Kaposi's Sarcoma, multiple myeloma, or renal cell cancer.

**[0078]** In another embodiment, HSA fusions with natriuretic peptides, including but not limited

to ANP-HSA fusions or BNP-HSA fusions, may be used for the treatment of cardiovascular disorders. For example, in a preferred embodiment, HSA fusions with natriuretic peptides, including but not limited to ANP-HSA fusions or BNP-HSA fusions, may be used for the treatment of congestive heart failure. In an additional preferred embodiment, HSA fusions with natriuretic peptides, including but not limited to ANP-HSA fusions or BNP-HSA fusions, may be used in the treatement of post-myocardial infarction. In additional embodiments, HSA fusions with natriuretic peptides, including but not limited to ANP-HSA fusions or BNP-HSA fusions, may be used to additional cardiovascular disorders, including, but not limited to hypertension, salt-sensitive hypertension, angina pectoris, peripherial artery disease, hypotension, cardiac volume overload, cardiac decompensation, cardiac failure, left ventricular dysfunction, dyspnea, myocardial reperfusion injury, or left ventricular remodeling. In another embodiment, HSA fusions with natriuretic peptides, including but not limited to ANP-HSA fusions or BNP-HSA fusions, may be used in the treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac ouput and/or hypertension. In further embodiments, HSA fusions with natriuretic peptides, including but not limited to ANP-HSA fusions or BNP-HSA fusions, may be used in the treatment of renal diseases, including, but not limited to diabetic nephrophathy; glomerular hypertrophy, glomerular injury, renal glomerular disease, actute and/or chronic renal failure. In an additional embodiment, HSA fusions with natriuretic peptides, including but not limited to ANP-HSA fusions or BNP-HSA fusions, may be used to treat stroke or excess fluid in tissues.

**[0079]** In an additional embodiment, HSA may be fused with natriuretic peptide variants including, but not limited to, BNP-HSA fusions wherein the BNP component of the fusion protein is BNP amino acid residues 1-29. In one embodiment, the BNP component of the HSA fusion protein consists of two BNP variants (e.g., BNP amino acid residues 1-29) in tandem. In another embodiment, the BNP component of the HSA fusion protein consists of three, four, five or more BNP variants (e.g., BNP amino acid residues 1-29) in tandem. In a preferred embodiment, HSA fusions with BNP variants (e.g., BNP amino acid residues 1-29) may be used for the treatment of congestive heart failure. In an additional preferred embodiment, HSA fusions with BNP variants (e.g., BNP amino acid residues 1-29) may be used in the treatment of post-myocardial infarction. In an additional embodiment, HSA fusions with BNP variants (e.g., BNP amino acid residues 1-29) may be used to treat additional cardiovascular disorders, including, but not limited to, hypertension, salt-sensitive hypertension, angina pectoris, peripheral artery disease, hypotension, cardiac volume overload, cardiac decompensation, cardiac failure, non-

hemodynamic CHF, left ventricular dysfunction, dyspnea, myocardial reperfusion injury, or left ventricular remodeling. In another embodiment, HSA fusions with BNP variants (e.g., BNP amino acid residues 1-29) may be used in the treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension. In a preferred embodiment, HSA fusion with BNP variants (e.g., BNP amino acid residues 1-29) may be used in the treatment of renal disorders or diseases, including, but not limited to, diabetic nephropathy; glomerular hypertrophy, glomerular injury, renal glomerular disease, acute and/or chronic renal failure. In an additional embodiment HSA fusions with BNP variants (e.g., BNP amino acid residues 1-29) may be used to treat stroke or excess fluid in tissues.

**[0080]** In related but distinct embodiments, the invention is directed to natriuretic peptide variants including, but not limited to BNP amino acid residues 1-29, wherein the peptides are not fused with HSA. In one embodiment, the BNP variants of the invention have the sequence of two BNP variants (e.g., BNP amino acid residues 1-29) in tandem. In an additional embodiment, the BNP variants of the invention have the sequence of three, four, five or more BNP variants (e.g., BNP amino acid residues 1-29) in tandem. In a preferred embodiment, the BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used for the treatment of congestive heart failure. In an additional preferred embodiment, the BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used in the treatment of post-myocardial infarction. In an additional embodiment, the BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used to treat additional cardiovascular disorders, including, but not limited to, hypertension, salt-sensitive hypertension, angina pectoris, peripheral artery disease, hypotension, cardiac volume overload, cardiac decompensation, cardiac failure, non-hemodynamic CHF, left ventricular dysfunction, dyspnea, myocardial reperfusion injury, or left ventricular remodeling. In another embodiment, the BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used in the treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension. In a further preferred embodiment, the BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used in the treatment of renal disorders or diseases, including, but not limited to, diabetic nephropathy; glomerular hypertrophy, glomerular injury, renal glomerular disease, acute and/or chronic renal failure. In an additional embodiment, the BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used to treat stroke or excess fluid in tissues.

**[0081]** In a further embodiment, the invention is directed to natriuretic peptide variants including, but not limited to, BNP variants (e.g., BNP amino acid residues 1-29), that have been modified in

order to extend half-life, biological activity, and/or to facilitate purification of the variant. According to this embodiment, the natriuretic peptide variants (e.g., BNP amino acid residues 1-29) may be pegylated, methylated, or otherwise chemically modified or conjugated using techniques known in the art. Alternatively, methods known in the art may be used to recombinantly fuse the natriuretic peptide variants of the invention to other peptide sequences known in the art to extend half-life, improve biological activity and/or facilitate purification. For example, natriuretic peptide variants of the invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a natriuretic variants (e.g., BNP amino acid residues 1-29) of the invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The natriuretic variants may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention (e.g., BNP amino acid residues 1-29) can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the variants to portions of IgA and IgM. Methods for fusing or conjugating the variants of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341(1992) (said references incorporated by reference in their entireties). In an additional embodiment, the modified BNP variants of the invention have the sequence of two BNP variants (e.g., BNP amino acid residues 1-29) in tandem. In an additional embodiment, the modified BNP variants of the invention have the sequence of three, four, five or more BNP variants (e.g., BNP amino acid residues 1-29) in tandem. In a preferred embodiment, the modified BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used for the treatment of congestive heart failure. In a preferred embodiment, the modified BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used in the treatment of post-myocardial infarction. In an additional embodiment, the modified BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used to treat additional cardiovascular disorders, including, but not limited to, hypertension, salt-sensitive hypertension, angina pectoris, peripheral artery disease, hypotension, cardiac volume overload, cardiac decompensation, cardiac failure, non-hemodynamic CHF, left ventricular dysfunction, dyspnea, myocardial reperfusion injury, or left ventricular remodeling. In another embodiment, the modified BNP variants (e.g., BNP amino acid residues 1-29) of the

invention may be used in the treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension. In a preferred embodiment, the modified BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used in the treatment of renal disorders or diseases, including, but not limited to, diabetic nephropathy; glomerular hypertrophy, glomerular injury, renal glomerular disease, acute and/or chronic renal failure. In an additional embodiment, the modified BNP variants (e.g., BNP amino acid residues 1-29) of the invention may be used to treat stroke or excess fluid in tissues.

**[0082]** In another embodiment, CNP-HSA fusions may be used in the regulation of endochodral ossification. For example, in a preferred embodiment, CNP-HSA fusions may be used in the treatment of skeletal dysplasias, including, but not limited to anchondroplasia, hypochondroplasia, and thanatophoric dysplasia.

**[0083]** As used herein, "therapeutic activity" or "activity" may refer to an activity whose effect is consistent with a desirable therapeutic outcome in humans, or to desired effects in non-human mammals or in other species or organisms. Therapeutic activity may be measured *in vivo* or *in vitro*. For example, a desirable effect may be assayed in cell culture. Such *in vitro* or cell culture assays are commonly available for many Therapeutic proteins as described in the art. Examples of assays include, but are not limited to those described herein in the Examples section or in the "Exemplary Activity Assay" column (column 3) of Table 1.

**[0084]** Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, such as cell surface and secretory proteins, are often modified by the attachment of one or more oligosaccharide groups. The modification, referred to as glycosylation, can dramatically affect the physical properties of proteins and can be important in protein stability, secretion, and localization. Glycosylation occurs at specific locations along the polypeptide backbone. There are usually two major types of glycosylation: glycosylation characterized by O-linked oligosaccharides, which are attached to serine or threonine residues; and glycosylation characterized by N-linked oligosaccharides, which are attached to asparagine residues in an Asn-X-Ser or Asn-X-Thr sequence, where X can be any amino acid except proline. N-acetylneuramic acid (also known as sialic acid) is usually the terminal residue of both N-linked and 0-linked oligosaccharides. Variables such as protein structure and cell type influence the number and nature of the carbohydrate units within the chains at different glycosylation sites. Glycosylation isomers are also common at the same site within a given cell type.

**[0085]** Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, as well as analogs and variants thereof, may be modified so that

glycosylation at one or more sites is altered as a result of manipulation(s) of their nucleic acid sequence, by the host cell in which they are expressed, or due to other conditions of their expression. For example, glycosylation isomers may be produced by abolishing or introducing glycosylation sites, *e.g.*, by substitution or deletion of amino acid residues, such as substitution of glutamine for asparagine, or unglycosylated recombinant proteins may be produced by expressing the proteins in host cells that will not glycosylate them, *e.g.* in *E. coli* or glycosylation-deficient yeast. These approaches are described in more detail below and are known in the art.

**[0086]** Therapeutic proteins, particularly those disclosed in Table 1, and their nucleic acid and amino acid sequences are well known in the art and available in public databases such as Chemical Abstracts Services Databases (e.g., the CAS Registry), GenBank, and subscription provided databases such as GenSeq (e.g., Derwent). Exemplary nucleotide sequences of Therapeutic proteins which may be used to derive a polynucleotide of the invention are shown in column 7, "SEQ ID NO:X," of Table 2. Sequences shown as SEQ ID NO:X may be a wild type polynucleotide sequence encoding a given Therapeutic protein (e.g., either full length or mature), or in some instances the sequence may be a variant of said wild type polynucleotide sequence (*e.g.*, a polynucleotide which encodes the wild type Therapeutic protein, wherein the DNA sequence of said polynucleotide has been optimized, for example, for expression in a particular species; or a polynucleotide encoding a variant of the wild type Therapeutic protein (i.e., a site directed mutant; an allelic variant)). It is well within the ability of the skilled artisan to use the sequence shown as SEQ ID NO:X to derive the construct described in the same row. For example, if SEQ ID NO:X corresponds to a full length protein, but only a portion of that protein is used to generate the specific CID, it is within the skill of the art to rely on molecular biology techniques, such as PCR, to amplify the specific fragment and clone it into the appropriate vector.

**[0087]** Additional Therapeutic proteins corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention include, but are not limited to, one or more of the Therapeutic proteins or peptides disclosed in the "Therapeutic Protein X" column of Table 1 (column 1), or fragment or variant thereof.

**[0088]** Table 1 provides a non-exhaustive list of Therapeutic proteins that correspond to a Therapeutic protein portion of an albumin fusion protein of the invention, or an albumin fusion protein encoded by a polynucleotide of the invention. The first column, "Therapeutic Protein X," discloses Therapeutic protein molecules that may be followed by parentheses containing scientific and brand names of proteins that comprise, or alternatively consist of, that Therapeutic protein molecule or a fragment or variant thereof. "Therapeutic protein X" as used herein may

refer either to an individual Therapeutic protein molecule, or to the entire group of Therapeutic proteins associated with a given Therapeutic protein molecule disclosed in this column. The "Biological activity" column (column 2) describes Biological activities associated with the Therapeutic protein molecule. Column 3, "Exemplary Activity Assay," provides references that describe assays which may be used to test the therapeutic and/or biological activity of a Therapeutic protein:X or an albumin fusion protein comprising a Therapeutic protein X (or fragment thereof) portion. Each of the references cited in the "Exemplary Activity Assay" column are herein incorporated by reference in their entireties, particularly with respect to the description of the respective activity assay described in the reference (see Methods section therein, for example) for assaying the corresponding biological activity set forth in the "Biological Activity" column of Table 1. The fourth column, "Preferred Indication: Y," describes disease, disorders, and/or conditions that may be treated, prevented, diagnosed, and/or ameliorated by Therapeutic protein X or an albumin fusion protein comprising a Therapeutic protein X (or fragment thereof) portion. The "Construct ID" column (column 5) provides a link to an exemplary albumin fusion construct disclosed in Table 2 which encodes an albumin fusion protein comprising, or alternatively consisting of the referenced Therapeutic Protein X (or fragment thereof) portion.

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| Interferon alpha (Interferon alfa-2b; Interferon alfa-2a; recombinant; Interferon alfa-n1; Interferon alfa-n3; Peginterferon alpha-2b; Ribavirin and interferon alfa-2b; Interferon alfacon-1; interferon consensus; YM 643; CIFN; interferon - alpha consensus; recombinant methionyl consensus interferon; recombinant consensus interferon; CGP 35269; RO 253036; RO 258310; INTRON A; PEG-INTRON; OIF; OMNIFERON; PEG-OMNIFERON; VELDONA; PEG-REBETRON; ROFERON A; WELLFERON; ALFERON N/LDO; REBETRON; ALTEMOL; VIRAFERONPEG; | Confers a range of cellular responses including antiviral, antiproliferative, antitumor and immunomodulatory activities; stimulate production of two enzymes: a protein kinase and an oligoadenylate synthetase. | Anti-viral assay: Rubinstein S, Familletti PC, Pestka S. (1981) Convenient assay for interferons. J. Virol. 37(2):755-8; Anti-proliferation assay: Gao Y, et al (1999) Sensitivity of an epstein-barr virus-positive tumor line, Daudi, to alpha interferon correlates with expression of a GC-rich viral transcript. Mol Cell Biol. 19(11):7305-13. | Viral infections include Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg virus; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not | 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, 4296. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| PEGASYS; VIRAFERON; VIRAFON; AMPLIGEN; INFERGEN; INFAREX; ORAGEN) | | | limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus; Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30 and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309). | | |
| Atrial natriuretic peptide (ANP; atrial natriuretic factor; ANF) | ANP is diuretic (natriuretic), hypotensive, and has an inhibitory effect on renin and aldosterone secretion. Involved in regulation of blood pressure and salt and water balance/ | Renin and aldosterone levels can be measured using methods known in the art, for example, in Yamato et al., Circ J 2003 May;67(5):384-90. Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., | Hypertension; salt-sensitive hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac | 3484, 4174. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | electrolyte homeostasis in body fluids. | Ultrasound Med Biol 2003 Mar;29(3):379-85. | decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular remodeling; post-myocardial infarction. | | |
| B-type natriuretic peptide (BNP, brain natriuretic peptide) | Stimulates smooth muscle relaxation and vasodilation, natriuresis,and suppression of renin-angiotensin and endothelin. | Inhibition of angiotensin can be determined using assays known in the art, for example using an in vitro proliferation assay with rat cardiac fibroblasts as described in Naunyn Schmiedebergs Arch Pharmacol 1999 May;359(5):394-9. Vasodilation can be measured in animals by measuring the myogenic responses of small renal arteries in an isobaric arteriograph system (*see* Am J Physiol Regul Integr Comp Physiol 2002 Aug;283(2):R349-R355). Natriuesis is determined by | Hypertension; salt-sensitive hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular | 3618, 3689, 3690, 3691, 3692, 3715, 3716, 3723, 3724, 3725, 3736, 3741, 3769, 3778, 3783, 3795, 3796, 3809, 3896, 3897, 3898, 3899, 3900, 3956, 3957, 3959, 3961, 3962, 3965, 3966, 3967, 3968, 4005, 4006, 4007, 4062, | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | | measuring the amount of sodium in the urine. | remodeling; post-myocardial infarction. | 4130, 4160, 4161, 4167, 4168, 4169, 4170, 4171, 4172, 4174. | |
| Long-acting natriuretic peptide (LANP; proANP-(31-67); | Inhibits renal $Na^+$-$K^+$-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of smooth muscle, as well as the dilation and constriction of blood vessels; inhibits plasma renin activity; causes diuresis and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection. | Renal $Na^+$-$K^+$-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of | Hypertension; salt-sensitive hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular remodeling; post-myocardial infarction. | 3886, 3887. | See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is incorporated by reference |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | | sodium in the urine. Diuresis is determined by measuring the amount of urine secreted. | | | |
| Vessel Dialator (VDP; proANP-(79-98)). | Inhibits renal $Na^+$-$K^+$-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of smooth muscle, as well as the dilation and constriction of blood vessels; inhibits aldosterone secretion; causes natriuresis in patients with congestive heart failure; causes kaliuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection. | Renal $Na^+$-$K^+$-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Aldosterone levels can be measured using methods known in the art, for example, in Yamato et al., Circ J 2003; May; 67(5):384-90. Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol | Hypertension; salt-sensitive hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular remodeling; post-myocardial infarction. | 3888, 3889. | See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | | 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Kaliuresis is determined by measuring the amount of potassium in the urine. | | | |
| Kaliuretic Peptide (KUP; proANP-(99-126)). | Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids. | Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted.. | Hypertension; salt-sensitive hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular remodeling; post-myocardial infarction. | 3890, 3891. | See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference |
| C-type Natriuretic Peptide | Promotes diuresis | Natriuesis is determined by | Hypertension; salt-sensitive | 3892, 3893. | See Table 2, |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| (CNP) | and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids. Involved in the regulation of endochondral ossification of bone. | measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted. cGMP production in bone can be measured using assays in the art (Yasoda et al., J. Biol. Chem. 1998; 273:11695-11700. | hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular remodeling; post-myocardial infarction; skeletal dysplasias including anchondroplasia, hypochondroplasia and thanatophoric dysplasia. | | SEQ ID NO:Z for particular construct. Also see, Vesely Am J Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference |
| *Dendroaspis* natriuretic peptide (DNP) | Inhibits $Na^+$-$K^+$-ATPase; enhances synthesis of prostaglandin E2 that regulates contraction and relaxation of | Renal $Na^+$-$K^+$-ATPase activity can be measured using assays known in the art, such as in Ku et al., 1987; Endocrinology 120:2166-2173. Vasodilation can be | Hypertension; salt-sensitive hypertension; congestive heart failure; angina pectoris, peripheral artery disease; diabetic nephropathy; stroke; kidney failure; acute and/or chronic renal failure; acute tubular | 3894, 3895. | See Table 2, SEQ ID NO:Z for particular construct. Also see, Vesely Am J |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | smooth muscle, as well as the dilation and constriction of blood vessels; inhibits aldosterone secretion; causes diuresis and natriuresis. Involved in regulation of blood pressure and salt/water/electrolyte balance in body fluids; renoprotection. | measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. Prostaglandin E2 synthesis can be determined using assays known in the art, (Cheng et al., J Endocrinol. 2004 Aug;182(2):249-56). Aldosterone levels can be measured using methods known in the art, for example, in Yamato et al., Circ J 2003 May; 67(5):384-90. Blood pressure can be measured with a sphygmomanometer or using other methods known in the art, such as in Reddy et al., Ultrasound Med Biol 2003 Mar; 29(3):379-85. Natriuesis is determined by measuring the amount of sodium in the urine. Diuresis is determined by measuring the amount of urine secreted. | necrosis; acute renal failure; renal disease; renal glomerular disease; excess fluid in tissues; hypotension; cardiac volume overload; cardiac decompensation; left ventricular dysfunction; dyspnea; treatment for elevated aldosterone levels, which can lead to vasoconstriction, impaired cardiac output and/or hypertension; cardiovascular disease; cardiac failure; myocardial reperfusion injury; left ventricular remodeling; post-myocardial infarction. | | Physiol Renal Rhysiol 2003; 285:F167-177 which is hereby incorporated by reference |
| Beta defensin-2 (beta defensin 4; SAP1; DEFB2; HBD-2; DEFB- | Involved in the innate defense system as an antimicrobial | Antimicrobial activity can be measured using assays known in the art, such as in Bals et | Treatment of fungal, bacterial, or viral infection; Infection in immune-compromised disease states; | 4173, 4175, 4176, 4177, 4178, 4179, | See Table 2, SEQ ID NO:Z for particular |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| 2; DEFB102; skin-antimicrobial peptide 1) | peptide; kills gram negative and gram positive organisms, such as, for example, E. coli, P. aeruginosa, S. aureus, E. faecalis, and Candida sp.; stimulates odontoblast differentiation | al., J. Clin. Invest. 1998 Sept 102(5):874-880. | Inflammation; Gingivitis; Bronchiolitis obliterans syndrome; Oral squamous cell carcinoma; Uterine infection; Psoriasis; Neonatal infection; Lung cancer; Inflammatory bowel Disease; Gastritis; Middle ear infection | 4180, 4181 | construct. |
| Human chemokine HCC-1 (ckBeta-1; CKB-1; HWFBD) | Involved in inflammation, allergy, tissue rejection, viral infection, and tumor biology; enhances proliferation of CD34+ myeloid progenitor cells. | Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ | Autoimmune disorders; Immunity; Vascular and Inflammatory disorders; HIV; AIDS; infectious diseases. | 1933, 1934, 1947, 1948, 1955, 1998, 2355, 2412, 2449, 2837, 2838, 2839, 2840, 2841, 2842, 2843, 2844, 2845, 2849, 2947, 3066, 3105, 3124, 3125, 3139, 3152, 3153, 3154, 3155, 3156, 3169, 3170, 3202, 3203, 3204, 3205, | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | | | | 3206, 3207, 3272, 3970. | |
| Fractalkine (neurotactin; chemokine CX3C) | Fractalkine is believed to play a role in chemotactic leukocyte migration and neurological disorders. | Fractalkine activity can be determined using Chemotactic leukocyte migration assays known in the art, for example: J. Immunol. Methods 33, ((1980)); Nature 1997 Jun 5;387(6633):611-7. | Immune disorders; Leukemia; Lymphoma; Bacterial or Yeast Infections | 4191, 4192, 4193, 4194. | See Table 2, SEQ ID NO:Z for particular construct |
| Oxyntomodulin | Stimulates insulin secretion; stimulates cAMP production; inhibits meal-stimulated gastric acid secretion; regulates gut motility; inhibits food intake. | The effect of oxyntomodulin on insulin secretion can be measured by methods known in the art, including the MIN6 cell assay described in Ann. NY Acad. Sci. 805:44-51 (1996).<br><br>cAMP accumulation can be measured using methods known in the art, including the *in vitro* assay described in Br J Pharmacol 138(4):660-70 (2003). | Most preferred: Hyperglycemia; Obesity; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X. | 3579, 3580, 4213, 4215, 4217, 4232, 4240, 4253. | See, Table 2, SEQ ID NO:Z for particular construct |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| Killer Toxin; Killer Toxin Peptide (KP) | A killer toxin (KT) produced by the yeast *Pichia anomala* is a glycoprotein capable of killing other microorganisms presenting specific cell wall receptors (KTR) and competing in natural habitats for the same ecological niche. Killer Toxin Peptide (KP) is a peptide derived from a recombinant antiidiotypic antibody, which retains killer toxin microbicidal activity, probably through the interaction with the beta-glucan killer toxin receptor on target microbial cells. | Candidacidal activity can measure in vitro using assays known in the art, such as those disclosed by Magliani et al., Nat. Biotechnol. 1997; 15:155-158; or by Polonelli et al, Clin. Diagn. Lab. Immunol. 1997; 4:142-146. | Candidiasis | 4227 | See, Table 2, SEQ ID NO:Z for particular construct |
| TIMP-4 (Tissue Inhibitor of Metalloprotease) | The proteins encoded by this gene family are natural inhibitors | TIMP inhibitory activity can be assayed using assays known in the art, such as | Anti-cancer applications; Restenosis; Autoimmune Disorders; Osteoarthritis | 4233, 4234, 4273, 4274 | See Table 2, SEQ ID NO:Z for particular |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | of the matrix metalloproteinases, a group of peptidases involved in degradation of the extracellular matrix. | those disclosed by Murphy et al., Biochem J 1981 Apr 1;195(1):167-70; Suneel et al., J Biol Chem 1995 Jun 16;270(24):14313-8. | | | construct |
| PYY (Peptide YY, including $PYY_{3-36}$ (amino acid residues 31-64 of full length PYY, amino acid residues 3-36 of mature PYY); also including PYY(3-36)(G9R) (SEQ ID NO:780)) | Decreases appetite; increases satiety; decreases food intake. | Appetite and food intake can be can be measured by methods known in the art (Batterham et al. Nature 2002; 418:650654) | Most preferred: Treatment of Obesity; treatment of Diabetes; suppression of body weight gain; suppression of appetite. Hyperglycemia; Diabetes; Diabetes Insipidus; Diabetes mellitus; Type 1 diabetes; Type 2 diabetes; Insulin resistance; Insulin deficiency; Hyperlipidemia; Hyperketonemia; Non-insulin dependent Diabetes Mellitus (NIDDM); Insulin-dependent Diabetes Mellitus (IDDM); A Condition Associated With Diabetes Including, But Not Limited To Obesity, Heart Disease, Hyperglycemia, Infections, Retinopathy, And/Or Ulcers; Metabolic Disorders; Immune Disorders; Obesity; Vascular Disorders; Suppression of Body Weight; Suppression of Appetite; Syndrome X. | 3108, 3109, 3281, 3117, 3118, 3282, 4215, 4235, 4236, 4262, 4267. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | | | Other indications for antibodies, antagonists: treatment of weight loss; treatment of AIDS wasting; appetite stimulant; treatment of cachexia. | | |
| Adrenomedullin | stimulates vasodilation; promotes bone growth. | Vasodilation can be measured using assays known in the art (Ashton et al. Pharmacology 2000; 61(2):101-105. The promotion of bone growth can be measured using assays known in the art, such as the osteoblast proliferation assay (Cornish et al. Am J Physiol 1997 Dec;273(6 Pt 1):E1113-20). | Treatment of Congestive Heart Failure; Hypertension; Myocardial Infarction; Septic Shock; Osteoporosis; Postmenopausal osteoporosis; Osteopenia. | 3144, 4239, 4260, 4261. | See Table 2, SEQ ID NO:Z for particular construct |
| Ghrelin | Stimulates release of growth hormone from anterior pituitary. Stimulates appetite and reduces fat burning. | Appetite and food intake can be can be measured by methods known in the art (Batterham et al. Nature 2002; 418:650654) | Endocrine; loss of body weight; loss of body weight associated with cancer or anorexia nervosa; loss of appetite; excessive appetite; body weight gain; Obesity; Diabetes; Acromegaly; Growth failure; Growth hormone deficiency; Growth failure and growth retardation Prader-Willi syndrome in children 2 years or older; Growth deficiencies; Growth failure associated with chronic renal | 4241, 4242, 4268. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | | | insufficiency; Postmenopausal osteoporosis; burns; cachexia; cancer cachexia; dwarfism; metabolic disorders; obesity; renal failure; Turner's Syndrome, pediatric and adult; fibromyalgia; fracture treatment; frailty, AIDS wasting | | |
| Calcitonin gene-related peptide (CGRP) | CGRP is a potent vasodilator, and a regulator of endothelial and osteoblast cell proliferation. Additional effects of CGRP include reduced gastric secretion, increased body temperature, anorexic effects, and positive inotropic and chronotropic effects on the heart | The vasodilatory activity of CGRP can be assayed using the aortic ring vasodilation assay described in Pharmacol Res. 1999 Mar;39(3):217-20. Endothelial and osteoblast cell proliferation activities can be measured in vitro (Eur J Pharmacol. 2000 Dec 15;409(3):273-8; Proc Natl Acad Sci U S A 1990 May;87(9):3299-303) | Migraine Headaches; Angina Pectoris; Arrythmias; Heart Failure; Hypertension; Postmenopausal Osteoporosis; Raynaud's Disease; Subarachnoid Haemorrhage | 4246, 4247, 4248, 4249. | See Table 2, SEQ ID NO:Z for particular construct. |
| Insulin-like growth factor-1 (Mecasermin; Somazon; IGF-1; IGF-1 complex; CEP 151; CGP 35126; FK 780; Mecar; RHIGF-I; Somatomedin-1; | IGF-I is a pleiotropic polypeptide with a wide range of actions in both central and peripheral nervous sytems. It is involved | IGF-I activity may be assayed in vitro using an serum withdrawal apoptosis-protection assay. (J Endocrinol 2000 Oct; 167(1):165-74). Proliferation | Diabetes mellitus; Growth disorders; Frailty; Amyotrophic lateral sclerosis; Osteoarthritis; Kidney disease & neuropathy; Dwarfism; HIV-1 infections; Myocardial ischaemia; Osteoporosis; Multiple | 4251, 4252. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| Somatomedin-C; SOMATOKINE; MYOTROPHIN; IGEF; DepoIGF-1) | in growth and development and protects neurons against cell death via the activation of intracellular pathways implicating phosphatidylinositide 3/Akt kinase. | assay using breast carcinoma cell line MCF-7 (Karey 1988 Cancer Res. 48: 4083) | sclerosis; Nerve disorders; Burns; diabetes; peripheral neuropathies | | |
| Neuraminidase (Influenza A virus (A/Goose/Guangdong/1/96(H5N1))) | Neuraminidase is one of two glycoproteins on the surface of the Influenza virus which, as an antigen defines the particular strain of virus. The variation of neuraminidase molecules over time permits the virus to evade human immune responses and therefore necessitates the formulation of a new vaccine each year. Neuraminidase cleaves the cellular- | Neuraminidase activity can be assayed in vitro using assays known in the art, such as those disclosed by Van Deusen et al., Avian Dis. 1983 Jul-Sep; 27(3):745-50; or by Wetherall et al., J. Clin. Microbiology 2003 Feb; 41(2):742-750. | Vaccine or antigen against Influenza A, strain H5N1; Avian Flu | 4254,4255 | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | receptor sialic acid residues to which the newly formed particles are attached. This cleavage releases the viruses, which can now invade new cells. Without neuraminidase, infection would be limited to one round of replication, rarely enough to cause disease. Neuraminidase may also facilitate viral invasion of the upper airways, possibly by cleaving the sialic acid moieties on the mucin that bathes the airway epithelial cells. | | | | |
| Hemagglutinin [Influenza A virus (A/Hong Kong/213/03(HK213:H5 N1))] | Hemagglutinin (HA), the major influenza virus surface glycoprotein, has two | Complement Fixation (CF) and Hemagglutination Inhibition (HI) can be assayed in vitro using assays known in | Vaccine or antigen against Influenza A, strain H5N1; Avian Flu | 4256, 4257. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | functions in infection: (i) it binds the virus to the cellular receptors, sialic acid residues of glycoproteins and glycolipids, and (ii) following endocytosis it mediates the low pH-induced fusion of viral and cellular membranes to permit entry of the viral genome into the cell. All influenza viruses bear two surface glycoproteins, a hemagglutinin and a neuraminidase, which are the antigens that define the particular strain of influenza. The variation of these molecules over time permits the virus to evade human | the art, such as those disclosed by Prince et al., Clin. Diagn. Lab. Immunol. 2003 May; 10(3):481-482. | | | |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | immune responses and therefore necessitates the formulation of a new vaccine each year. The hemagglutinin is a sialic acid receptor–binding molecule and mediates entry of the virus into the target cell. | | | | |
| Butyrylcholinesterase (BchE, Serum Cholinesterase, pseuocholinesterase E1 (CHE1)) | Butyrylcholinesterase accelerates cocaine metabolism: in vitro and in vivo effects in nonhuman primates and humans. Carmona GN, Jufer RA, Goldberg SR, Gorelick DA, Greig NH, Yu QS, Cone EJ, Schindler CW. Drug Metab Dispos. 2000 Mar;28(3):367-71. An atypical form of butyrylcholinesterase or the absence of its | BchE activity assay "Differential inhibition of human serum cholinesterase with fluoride: recognition of two new phenotypes." Nature 191: 496-498, 1961. "A rare genetically determined variant of pseudocholinesterase in two German families with high plasma enzyme activity." Europ. J. Biochem. 99: 65-69, 1979. "Genetic analysis of a Japanese patient with butyrylcholinesterase deficiency." Ann. Hum. Genet. 61:491-496, 1997. | Detoxification for Cocaine Overdose; suxamethonium sensitivity; apnea; | 4258, 4259. | See Table 2, SEQ ID NO:Z for particular construct. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | activity leads to prolonged apnea following administration of the muscle relaxant suxamethonium. The widespread expression of CHE1 in early differentiation suggests development-related functions for this protein. | | | | |
| Endothelin (ET-1; Genbank Accession No. NP_001946) | Endothelin is a potent vasoconstrictor. It is inappropriately elevated in hypertensive diseases and in heart failure.<br><br>Potent agonist for the ETA and ETB endothelin receptors. Induces the production of hypoxia-inducible factor 1α, and, thus, | Endothelin-1-induced vasoconstriction is mediated by Ca2+ influx through a non-selective cation channel. It is mediated by the endothelin receptors ETA and ETB, both of which are G-protein-coupled receptors. Antagonists can be identified by their ability to prevent Ca-flux mediated by ET-1 peptide, which can be assayed in vitro using assays known in art, such as disclosed in | CHF, pulmonary hypertension, hypertension, renal failure, any disease for which endothelin antagonism would be beneficial, as anti-angiogenic or anti-tumor agent for treatment of cancer and macular degeneration. | | SEQ ID NOs: 781 and 782. |

**Table 1**

| Therapeutic Protein:X | Biological Activity | Exemplary Activity Assay | Preferred Indication:Y | Construct ID | Therapeutic Protein:Z |
|---|---|---|---|---|---|
| | the production of VEGF. | Wong-Dusting et al, J. Cardiovasc. Pharmacol. (1991) 17:S236-S238; Ono et al., Nature (1994) 370:252-253; Koyama, Y. et al., Neuroscience (2000) 101:219-227; Russell, F.D. and Molenaar, P., Trends Pharmacol. Sci. (2000) 21:353-359; Masaki, T. et al., Eur. J. Pharmacol. (1999) 375:133-138; Inoue, A. et al., Proc. Natl. Acad. Sci. USA (1989) 86:2863-2867; and Spinella, F. et al., J. Biol. Chem. (2002) 277:27850-27855. | | | |
| Mechano Growth Factor (MGF; IGF-IEc; Genbank Accession No. P05019) | A muscle growth factor that appears lost with aging. Can also act as neuroprotective agent. Unlike mature IGF-I, MGF inhibits terminal differentiation whilst increasing myoblast proliferation. | Myoblast proliferation and differentiation can be assayed in vitro by assays known in the art such as disclosed in Dluzniewska et al, FASEB J. (2005) Sep 6; Goldspink G. J Musculoskelet Neuronal Interact. (2004) Jun;4(2):143-7; or Yang SY and Goldspink G, FEBS Lett. (2002) Jul 3, 522(1-3):156-60. | Wasting disease, cachexia, stroke, MI, CHF, diseases where neuroprotection or muscle (skeletal or smooth) protection or regeneration would be beneficial. | | SEQ ID NOs: 783 and 784. |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3422 | pSAC35:APsp.HSA.IFNa | Acid Phosphatase signal peptide followed by mature HSA and IFNa. | pSAC35 | 192 | 117 | 267 | 342 | 343 | Acid phoshpatase |
| 2 | 3423 | pSAC35:INVsp.HSA.IFNa | Invertase signal peptid followed by mature HSA and IFNa. | pSAC35 | 193 | 118 | 268 | 344 | 345 | Invertase |
| 3 | 3424 | pSAC35:KTsp.HSA.IFNa | Killer Toxin signal peptide followed by mature HSA and IFNa. | pSAC35 | 194 | 119 | 269 | 346 | 347 | Killer toxin |
| 4 | 2249 | pSAC35:IFNa2-HSA also named: pSAC23:IFNα2-HSA | Mature IFNa2 fused upstream of mature HSA and downstream of HSA/kex2 leader sequence. | pSAC35 | 195 | 120 | 270 | 348 | 349 | HSA/kex2 |
| 5 | 2343 | pSAC35.INV-IFNA2.HSA | Mature Interferon alpha2 fused upstream of mature HSA and downstream of invertase signal peptide. | pSAC35 | 196 | 121 | 271 | 350 | 351 | invertase |
| 6 | 2366 | pSAC35.MAF-IFNa2.HSA | Mature IFNa2 fused upstream of mature HSA and downstream of yeast mating factor alpha leader sequence. | pSAC35 | 197 | 122 | 272 | 352 | 353 | MFα-1 |
| 7 | 2381 | pC4:HSA-IFNa2(C17-E181) | Amino acids C17 to E181 of IFNa2 (fragment shown as amino acids C1 to E165 of SEQ ID NO:273) fused downstream of HSA. | pC4 | 198 | 123 | 273 | 354 | 355 | HSA |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 2382 | pC4:IFNa2-HSA | IFNa2 fused upstream of mature HSA. | pC4 | 199 | 124 | 274 | 356 | 357 | Native IFNα2 leader |
| 9 | 2410 | pSAC35INV:IFNa-HSA | Mature IFNa2 fused downstream of the invertase signal peptide and upstream of mature HSA. | pSAC35 | 200 | 125 | 275 | 358 | 359 | invertase |
| 10 | 3165 | pSAC35:HSA.IFNa also named CID 3165, pSAC35:HSA.INFa | HSA fused upstream of IFNα and downstream of the HSA/kex2 leader. | pSAC35 | 201 | 126 | 276 | None | None | HSA/kex2 |
| 11 | 3476 | pSAC35:G19Rsp.HSA.IFNa | The Modified HSA/kex2 signal sequence followed by mature HSA followed by INF-alpha. | pSAC35 | 202 | 127 | 277 | 360 | 361 | Modified HSA/Kex2 |
| 12 | 3690 | pC4:MPIFSP.BNP/HSA | Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by BNP fused to the N-terminus of mature HSA. | pC4 | 203 | 128 | 278 | 362 | 363 | MPIF-1 |
| 13 | 3691 | pC4:SPCON.BNP/HSA | A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA. | pC4 | 204 | 129 | 279 | 364 | 365 | Consensus |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 3715 | pSAC35:BNP29/HSA.S65 | A single copy of human BNP (amino acids 1-29) fused to the N-terminus of HSA (S65-L585), an HSA N-terminal truncation (delta 1-64). This is downstream of the HSA/Kex2 signal sequence. | pSAC35 | 205 | 130 | 280 | 366 | 367 | HSA/Kex2 |
| 15 | 3723 | pEE12.1:MPIFSP.BNP/HSA | Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by BNP fused to the N-terminus of mature HSA. | pEE12.1 | 206 | 131 | 281 | None | None | MPIF-1 |
| 16 | 3724 | pEE12.1:SPCON.BNP/HSA | A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA. | pEE12.1 | 207 | 132 | 282 | None | None | Consensus |
| 17 | 3725 | pEE12.1:SPCON2.BNP/HSA | A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA. | pEE12.1 | 208 | 133 | 283 | None | None | Consensus Signal Peptide #2 |
| 18 | 3736 | pC4:SPCON2.BNP/HSA | A consensus signal sequence followed by BNP fused to the N-terminus of mature HSA. | pC4 | 209 | 134 | 284 | 368 | 369 | Consensus Signal Peptide #2 |
| 19 | 3769 | pC4:BNP(R13G)/HSA | Myeloid progenitor inhibitory factor-1 (MPIF) signal sequence followed by BNP mutant (R13G) fused to the N-terminus of mature HSA. | pC4 | 210 | 135 | 285 | 370 | 371 | MPIF-1 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 3778 | pC4:SPCON.BNP29/ HSA.S65 | A single copy of human BNP (1-29) fused to the N-terminus of HSA (S65-L585), an HSA N-terminal truncation (delta 1-64). This is downstream of a consensus signal sequence. | pC4 | 211 | 136 | 286 | 372 | 373 | Consensus |
| 21 | 3783 | pC4:SPCON.BNP(R 13G)/HSA | Consensus signal sequence followed by BNP mutant (R13G) fused to the N-terminus of mature HSA. | pC4 | 212 | 137 | 287 | 374 | 375 | Consensus |
| 22 | 3795 | pC4:SPCON.BNP(K 14G)/HSA | Consensus signal sequence followed by BNP mutant (K14G) fused to the N-terminus of mature HSA. | pC4 | 213 | 138 | 288 | 376 | 377 | Consensus |
| 23 | 3796 | pSAC35:HSA/BNP | Followed by mature HSA fused to the N-terminus of BNP. | pSAC35 | 214 | 139 | 289 | 378 | 379 | HSA/Kex2 |
| 24 | 3809 | pSAC35:BNP30(GG G)/HSA | HSA/Kex2 signal sequence followed by BNP (amino acids 1-30) fused via tripartite glycines to the N-terminus of mature HSA. | pSAC35 | 215 | 140 | 290 | 380 | 381 | HSA/Kex2 |
| 25 | 3886 | pSAC35:HSA/KEX2 .LANP.HSA | HSA/Kex2 signal sequence followed by LANP fused to the N-terminus of mature HSA. LANP corresponds to amino acids 26-55 of SeqID No:291 (hereby referred to as LANP). | pSAC35 | 216 | 141 | 291 | None | None | HSA/Kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 26 | 3887 | pSAC35:HSA/KEX2 .HSA.LANP | HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature LANP. | pSAC35 | 217 | 142 | 292 | None | None | HSA/Kex2 |
| 27 | 3888 | pSAC35:HSA/KEX2 .VDP.HSA | HSA/Kex2 signal sequence followed by VDP fused to the N-terminus of mature HSA. VDP corresponds to amino acids 56-92 of SeqID No:293 (hereby referred to as VDP). | pSAC35 | 218 | 143 | 293 | None | None | HSA/Kex2 |
| 28 | 3889 | pSAC35:HSA/KEX2 .HSA.VDP | HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature VDP. | pSAC35 | 219 | 144 | 294 | None | None | HSA/Kex2 |
| 29 | 3890 | pSAC35:HSA/KEX2 .KUP.HSA | HSA/Kex2 signal sequence followed by KUP fused to the N-terminus of mature HSA. KUP corresponds to amino acids 104-123 of SeqID No:295 (hereby referred to as KUP). | pSAC35 | 220 | 145 | 295 | None | None | HSA/Kex2 |
| 30 | 3891 | pSAC35:HSA/KEX2 .HSA.KUP | HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature KUP. | pSAC35 | 221 | 146 | 296 | None | None | HSA/Kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 31 | 3892 | pSAC35:HSA/KEX2 .CNP.HSA | HSA/Kex2 signal sequence followed by CNP fused to the N-terminus of mature HSA. CNP corresponds to amino acids 105-123 of SeqID No:297 (hereby referred to as KUP). | pSAC35 | 222 | 147 | 297 | None | None | HSA/Kex2. |
| 32 | 3893 | pSAC35:HSA/KEX2 .HSA.CNP | HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature CNP. | pSAC35 | 223 | 148 | 298 | None | None | HSA/Kex2 |
| 33 | 3894 | pSAC35:HSA/KEX2 .DNP.HSA | HSA/Kex2 signal sequence followed by DNP fused to the N-terminus of mature HSA. | pSAC35 | 224 | 149 | 299 | None | None | HSA/Kex2 |
| 34 | 3895 | pSAC35:HSA/KEX2 .HSA.DNP | HSA/Kex2 signal sequence followed by mature HSA fused to the N-terminus of mature DNP. | pSAC35 | 225 | 150 | 300 | None | None | HSA/Kex2 |
| 35 | 3618 | pC4:SPCON.BNP1-32(2x)/HSA | A consensus signal sequence followed by two, tandem copies of mature BNP fused to the N-terminus of mature HSA. | pC4 | 226 | 151 | 301 | 382 | 383 | Consensus |
| 36 | 3484 | pSAC35:ANP/HSA | HSA/kex2 leader followed by atrial natriuretic peptide followed by mature HSA. | pSAC35 | 227 | 152 | 302 | 384 | 385 | HSA/kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 37 | 1933 | pSAC35:HCC-1.T20-N93:HSA | Amino acids T20 to N93 of HCC-1 fused upstream of mature HSA and downstream of the HSA/kex2 leader sequence. | pSAC35 | 228 | 153 | 303 | 386 | 387 | HSA/kex2 |
| 38 | 1934 | pSAC35:HCC-1C.O.T20-N93:HSA | Amino acids T20 to N93 of HCC-1 fused upstream of mature HSA and downstream of the HSA/kex2 leader sequence. DNA sequence is codon optimized for yeast expression. | pSAC35 | 229 | 154 | 304 | 388 | 389 | HSA/kex2 |
| 39 | 1947 | pSAC35:d8HCC-1.G28-N93:HSA | Amino acids G28 to N93 of HCC-1 fused upstream of mature HSA and downstream of HSA/kex2 leader sequence. | pSAC35 | 230 | 155 | 305 | 390 | 391 | HSA/kex2 |
| 40 | 1948 | pSAC35:d8HCC-1C.O.G28-N93:HSA | Amino acids G28 to N93 of HCC-1 fused upstream of mature HSA and downstream of HSA/kex2 leader sequence. DNA sequence is codon optimized for yeast expression. | pSAC35 | 231 | 156 | 306 | 392 | 393 | HSA/kex2 |
| 41 | 1955 | pSAC35:t9HCC-1.G28-N93:spcHSA | Amino acids G28 to N93 of HCC-1 fused upstream of a 16 amino acid spacer and mature HSA and downstream of HSA/kex2 leader sequence. | pSAC35 | 232 | 157 | 307 | 394 | 395 | HSA/kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 42 | 1998 | pC4:CKB1.G28-N93.HSA | Amino acids G28 to N93 of CkBeta1 fused upstream of mature HSA and downstream of the HSA leader sequence. | pC4 | 233 | 158 | 308 | 396 | 397 | HSA |
| 43 | 2355 | pSAC35:MATalpha.d8ckbeta1.G28-N93:HSA | Amino acids G28 to N93 of Ckbeta1 fused upstream of mature HSA and downstream of the yeast mating factor alpha leader sequence. | pSAC35 | 234 | 159 | 309 | 398 | 399 | MFα-1 |
| 44 | 2412 | pSAC35:delKEX.d8ckbeta1.G28-N93:HSA | Amino acids G28 to N93 of Ckbeta1 fused downstream of the HSA signal sequence (with the KEX site deleted – last 6 amino acids of the leader) and upstream of mature HSA. | pSAC35 | 235 | 160 | 310 | 400 | 401 | HSA minus the KEX site |
| 45 | 2449 | pSAC35:INV.d8CKB1.G28-N93:HSA | Amino acids G28 to N93 of Ckbeta1 fused downstream of the invertase signal peptide and upstream of mature HSA. | pSAC35 | 236 | 161 | 311 | 402 | 403 | Invertase |
| 46 | 2837 | pSAC35:CKB1.K21-N93:HSA | K21-N93 of CKB1 (fragment shown as K2 to N74 of SEQ ID NO:1735) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 237 | 162 | 312 | 404 | 405 | HSA/kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 47 | 2838 | pSAC35:CKB1.T22-N93:HSA | T22-N93 of CKB1 (fragment shown as T3 to N74 of SEQ ID NO:1736) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 238 | 163 | 313 | 406 | 407 | HSA/kex2 |
| 48 | 2839 | pSAC35:CKB1.E23-N93:HSA | E23-N93 of CKB1 (fragment shown as E4 to N74 of SEQ ID NO:1737) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 239 | 164 | 314 | 408 | 409 | HSA/kex2 |
| 49 | 2840 | pSAC35:CKB1.S24-N93:HSA | S24-N93 of CKB1 (fragment shown as S5 to N74 of SEQ ID NO:1738) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 240 | 165 | 315 | 410 | 411 | HSA/kex2 |
| 50 | 2841 | pSAC35:CKB1.S25-N93:HSA | S25-N93 of CKB1 (fragment shown as S6 to N74 of SEQ ID NO:1739) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 241 | 166 | 316 | 412 | 413 | HSA/kex2 |
| 51 | 2842 | pSAC35:CKB1.S26-N93:HSA | S26-N93 of CKB1 (fragment shown as S7 to N74 of SEQ ID NO:1740) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 242 | 167 | 317 | 414 | 415 | HSA/kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 52 | 2843 | pSAC35:CKB1.R27-N93:HSA | R27-N93 of CKB1 (fragment shown as R8 to N74 of SEQ ID NO:1741) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 243 | 168 | 318 | 416 | 417 | HSA/kex2 |
| 53 | 2844 | pSAC35:CKB1.P29-N93:HSA | P29-N93 of CKB1 (fragment shown as P10 to N74 of SEQ ID NO:1742) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 244 | 169 | 319 | 418 | 419 | HSA/kex2 |
| 54 | 2845 | pSAC35:CKB1.Y30-N93:HSA | Y30-N93 of CKB1 (fragment shown as Y11 to N74 of SEQ ID NO:1743) fused downstream of the HSA/kex2 leader and upstream of mature HSA. | pScCHSA | 245 | 170 | 320 | 420 | 421 | HSA/kex2 |
| 55 | 2849 | pC4.MPIFsp.CKB1.G28-N93.HSA | G28-N93 of CKB1 (fragment shown as G9 to N74 of SEQ ID NO:1744) fused downstream of the MPIF signal peptide and upstream of mature HSA. | pC4 | 246 | 171 | 321 | 422 | 423 | MPIF |
| 56 | 2947 | pSAC:CKb-1δ8(x2).HSA | Invertase signal peptide followed by amino acids G28-N93 of full length CKβ1 (SEQ IDNO:1769), tandemly repeated, followed by mature HSA. | pSAC35 | 247 | 172 | 322 | 424 | 425 | Invertase |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 57 | 3066 | pSAC35:CKB-1d8.GLP-1(7-36).HSA | Invertase signal peptide followed by amino acids G28-N93 of full length CKβ1 (SEQ IDNO:1788), followed by GLP-1(7-36), followed by mature HSA. | pScCHSA | 248 | 173 | 323 | 426 | 427 | invertase |
| 58 | 3105 | pSAC35:INV.t9HCC-1.G28-N93:spc.HSA | Invertase signal peptide followed by amino acids G28 to N93 of HCC-1 fused upstream of a spacer and mature HSA. | pSAC35 | 249 | 174 | 324 | 428 | 429 | Invertase |
| 59 | 3124 | pSAC35:INV.CKB1.P29-N93:HSA | Invertase signal peptide followed by amino acids 29 to 93 of full length ckbeta1 fused to N-terminus of HSA. | pSAC35 | 250 | 175 | 325 | 430 | 431 | invertase |
| 60 | 3125 | pSAC35:INV.CKb-1.R27-N93:HSA | Invertase signal peptide followed by amino acids 27 to 93 of full length ckbeta1 fused to N-terminus of HSA. | pSAC35 | 251 | 176 | 326 | 432 | 433 | invertase |
| 61 | 3139 | pSAC35:INV.CKB1.G28-N93.DAHK.HSA | Invertase signal peptide followed by amino acids G28-N93 of full length CKβ1 (see, e.g, SEQ IDNO:1788), followed by a 16 amino acid linker derived from the N-terminus of HSA, followed by mature HSA. | pSAC35 | 252 | 177 | 327 | 434 | 435 | Invertase |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 62 | 3152 | pSAC35:INV.CKB1. Met.R27-N93.HSA | Invertase signal peptide followed by a Met, followed by amino acids R27-N93 of full length CKβ1, followed by mature HSA. | pSAC35 | 253 | 178 | 328 | 436 | 437 | invertase |
| 63 | 3153 | pSAC35:INV.CKB1. Met.S26-N93.HSA | Invertase signal peptide followed by a Met, followed by amino acids S26-N93 of full length CKβ1, followed by mature HSA. | pSAC35 | 254 | 179 | 329 | 438 | 439 | Invertase |
| 64 | 3154 | pSAC35:INV.CKB1. Met.S25-N93.HSA | Invertase signal peptide followed by a Met, followed by amino acids S25-N93 of full length CKβ1, followed by mature HSA. | pSAC35 | 255 | 180 | 330 | 440 | 441 | invertase |
| 65 | 3155 | pSAC35:INV.CKB1. Met.G28-N93.HSA | Invertase signal peptide followed by a Met, followed by amino acids G28-N93 of full length CKβ1, followed by mature HSA. | pSAC35 | 256 | 181 | 331 | 442 | 443 | invertase |
| 66 | 3156 | pSAC35:INV.CKB1. Met.P29-N93.HSA | Invertase signal peptide followed by a Met, followed by amino acids P29-N93 of full length CKβ1, followed by mature HSA. | pSAC35 | 257 | 182 | 332 | 444 | 445 | invertase |
| 67 | 3169 | pSAC35:KT.CKB1. G28-N93.HSA | Killer toxin signal sequence fused upstream of amino acids G28 through N93 of CKB1 (fragment shown as amino acids G1 to N66 of SEQ ID NO:1822) and mature HSA. | pSAC35 | 258 | 183 | 333 | None | None | Killer toxin |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 68 | 3170 | pSAC35:KT.HA.CKB1.G28-N93.HSA | Killer toxin signal sequence followed by HA dipeptide and amino acids G28 through N93 of CKB1 (fragment shown as amino acids G1 to N66 of SEQ ID NO:1823) and mature HSA. | pSAC35 | 259 | 184 | 334 | None | None | Killer toxin |
| 69 | 3202 | pSAC35:API.d8CKb1/HSA | HSA/kex2 leader followed by amino acids "API" followed by d8CKb1 and mature HSA. The sequence of delta 8 for CKB1 is shown in SEQ ID NO:1833. | pSAC35 | 260 | 185 | 335 | 446 | 447 | HSA/kex2 |
| 70 | 3203 | pSAC35:ASL.d8CKb1/HSA | HSA/kex2 leader followed by amino acids "ASL" followed by d8CKb1 and mature HSA. | pSAC35 | 261 | 186 | 336 | 448 | 449 | HSA/kex2 |
| 71 | 3204 | pSAC35:SPY.d8CKb1/HSA | HSA/kex2 leader followed by amino acids "SPY" followed by d8CKb1 and mature HSA. | pSAC35 | 262 | 187 | 337 | 450 | 451 | HSA/kex2 |
| 72 | 3205 | pSAC35:MSPY.d8CKb1/HSA | HSA/kex2 leader followed by amino acids "MSPY" followed by d8CKb1 and mature HSA. | pSAC35 | 263 | 188 | 338 | 452 | 453 | HSA/kex2 |
| 73 | 3206 | pSAC35:CPYSC.d8CKb1/HSA | HSA/kex2 leader followed by a five amino acid linker followed by d8CKb1 and mature HSA. | pSAC35 | 264 | 189 | 339 | 454 | 455 | HSA/kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 74 | 3207 | pSAC35:GPY.d8CKb1/HSA | HSA/kex2 leader followed by amino acids "GPY" followed by d8CKb1 and mature HSA. | pSAC35 | 265 | 190 | 340 | 456 | 457 | HSA/kex2 |
| 75 | 3272 | pSAC35.INV:{D}8CK{b}1(x2)/HSA | CKbeta-1 tandem repeat (x2) fusion to the N-termal HSA. Under the invertase signal peptide. | pSAC35 | 266 | 191 | 341 | 458 | 459 | Invertase |
| 76 | 3692 | pC4:MPIFSP.cynoBNP/CSA | Myeloid progenitor inhibitory factor-1 (MPIF-1) signal sequence followed by cynomolgus monkey BNP fused at the N-terminus of cynomolgus monkey serum albumin. | pC4 (Mammalian) | 496 | 460 | 532 | 568 | 569 | MPIF-1 |
| 77 | 3716 | pC4:ratBNP45/RSA | Pre-pro region of the HSA leader sequence followed by rat BNP(1-45) fused at the N-terminus of rat serum albumin. | pC4 (Mammalian) | 497 | 461 | 533 | 570 | 571 | HSA |
| 78 | 3741 | pC4:MPIFSP.ratBNP45/RSA | Myeloid progenitor inhibitory factor-1 (MPIF-1) signal sequence followed by rat BNP(1-45) fused at the N-terminus of rat serum albumin. | pC4 (Mammalian) | 498 | 462 | 534 | 572 | 573 | MPIF-1 |
| 79 | 3956 | pSAC35:BNP(K3-H32).HSA | HSA/Kex2 signal sequence followed by BNP (amino acids 3-32) fused at the N-terminus of mature HSA. | pSAC35 | 499 | 463 | 535 | 574 | 575 | HSA/Kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 80 | 3957 | pSAC35:BNP(K3-R30).GGG.HSA | HSA/Kex2 signal sequence followed by BNP (amino acids 3-30) fused via tripartite glycines to the N-terminus of mature HSA. | pSAC35 | 500 | 464 | 536 | 576 | 577 | HSA/Kex2 |
| 81 | 3959 | pSAC35:HSA.BNP(S1-L29) | HSA/Kex2 signal sequence followed by mature HSA fused to BNP (amino acids 1-29) at its C-terminus. | pSAC35 | 501 | 465 | 537 | 578 | 579 | HSA/Kex2 |
| 82 | 3960 | pSAC35:HSA.IFNalpha2a | HSA/Kex2 signal sequence followed by mature HSA fused to interferon alpha 2a at its C-terminus. | pSAC35 | 502 | 466 | 538 | 580 | 581 | HSA/Kex2 |
| 83 | 3961 | pSAC35:HSA.(BNP(S1-L29))x2 | HSA/Kex2 signal sequence followed by mature HSA fused to two tandem copies of BNP (amino acids 1-29) at its C-terminus. | pSAC35 | 503 | 467 | 539 | 582 | 583 | HSA/Kex2 |
| 84 | 3962 | pcDNA3.1-:BNP(1-32).HSA | Pre-pro region of the HSA signal sequence followed by BNP (amino acids 1-32) fused at the N-terminus of mature HSA. | pCDNA3.1 | 504 | 468 | 540 | None | None | HSA |
| 85 | 3965 | pSAC35:HSA.BNP(S1-R30) | HSA/Kex2 signal sequence followed by mature HSA fused to BNP (amino acids 1-30) at its C-terminus. | pSAC35 | 505 | 469 | 541 | 584 | 585 | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 86 | 3966 | pSAC35:HSA.BNP(S1-R31) | HSA/Kex2 signal sequence followed by mature HSA fused to BNP (amino acids 1-31) at its C-terminus. | pSAC35 | 506 | 470 | 542 | 586 | 587 | HSA/Kex-2 |
| 87 | 3967 | pSAC35:HSAsp.BNP(S1-H32).HSA | Pre region of the HSA signal sequence followed BNP (amino acids 1-32) fused to the N-terminus of mature HSA. | pSAC35 | 507 | 471 | 543 | None | None | HSA |
| 88 | 3968 | pSAC35:INVsp.BNP(S1-H32).HSA | Invertase signal peptide followed by BNP (amino acids 1-32) fused to the N-terminus of mature HSA. | | 508 | 472 | 544 | 588 | 589 | Invertase |
| 89 | 3970 | pSAC35:INVsp.CKB1(T20-N93)(E34A).HSA | Invertase signal peptide followed by mature mutant Ckbeta1 (amino acids 20-93 (E34A)) fused to the N-terminus of mature HSA. | pSAC35 | 509 | 473 | 545 | 590 | 591 | Invertase |
| 90 | 4005 | pSAC35:BNP(S1-R30).HSA | HSA/Kex-2 signal sequence followed by BNP (amino acids 1-30) fused to the N-terminus of mature HSA. | pSAC35 | 510 | 474 | 546 | None | None | HSA/Kex-2 |
| 91 | 4006 | pSAC35:BNP(S1-R30).HSA(D25-E40).HSA | HSA/Kex-2 signal sequence followed by BNP (amino acids 1-30) fused via a 16 amino acid linker derived from HSA (amino acids 25-40) to the N-terminus of mature HSA. | pSAC35 | 511 | 475 | 547 | None | None | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 92 | 4007 | pSAC35:BNP(S1-R30).HSA(D25-Q56).HSA | HSA/Kex-2 signal sequence followed by BNP (amino acids 1-30) fused via a 32 amino acid linker derived from HSA (amino acids 25-56) to the N-terminus of mature HSA. | pSAC35 | 512 | 476 | 548 | None | None | HSA/Kex-2 |
| 93 | 4062 | pcDNA3.1:MPIFsp.HSA.BNP(S1-H32) | Myeloid progenitor inhibitory factor-1 (MPIF-1) signal sequence followed by mature HSA fused to BNP at its C-terminus. | pCDNA3.1- | 513 | 477 | 549 | None | None | MPIF-1 |
| 94 | 4130 | pSAC35:HSA (C34S)-BNP (1-29) | HSA/Kex-2 signal sequence followed by a mutant of mature HSA (C34S) fused to BNP at its C-terminus. | pSAC35 | 514 | 478 | 550 | None | None | HSA/Kex-2 |
| 95 | 4160 | pSAC35:BNP(S1-R30:P2A).HSA | HSA/Kex-2 followed by a mutant BNP (amino acids 1-30 (P2A)) fused to the N-terminus of mature HSA. | pSAC35 | 515 | 479 | 551 | None | None | HSA/Kex-2 |
| 96 | 4161 | pSAC35:BNP(S1-R30:P2L).HSA | HSA/Kex-2 followed by a mutant BNP (amino acids 1-30 (P2L)) fused to the N-terminus of mature HSA. | pSAC35 | 516 | 480 | 552 | None | None | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 97 | 4167 | pSAC35:DSA.dogBNP(1-32) | Modified HSA/Kex-2 signal sequence followed by dog serum albumin fused to dog BNP (amino acids 1-32) at its C-terminus. | pSAC35 | 517 | 481 | 553 | None | None | Modified HSA/Kex-2 |
| 98 | 4168 | pSAC35:DSA.dogBNP(1-29) | Modified HSA/Kex-2 signal sequence followed by dog serum albumin fused to dog BNP (amino acids 1-29) at its C-terminus. | pSAC35 | 518 | 482 | 554 | None | None | Modified HSA/Kex-2 |
| 99 | 4169 | pSAC35:KTsp.CSA.cynoBNP(1-29) | Killer toxin signal sequence followed by cynomolgus monkey serum fused to cyno BNP (1-29) at its C-terminus. | pSAC35 | 519 | 483 | 555 | None | None | Killer toxin |
| 100 | 4170 | pSAC35:KTsp.RSA.ratBNP(1-45) | Killer toxin signal sequence followed by rat serum albumin fused to rat BNP (amino acids 1-45) at its C-terminus. | pSAC35 | 520 | 484 | 556 | None | None | Killer toxin |
| 101 | 4171 | pSAC35:KTsp.RSA.ratBNP(14-42) | Killer toxin signal sequence followed by rat serum albumin fused to rat BNP (amino acids 14-42) at its C-terminus. | pSAC35 | 521 | 485 | 557 | None | None | Killer toxin |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 102 | 4172 | pSAC35:MSA.mouse BNP(1-45) | Invertase signal sequence followed by mouse serum albumin fused to mouse BNP (amino acids 1-45) at its C-terminus. | pSAC35 | 522 | 486 | 558 | None | None | Invertase |
| 103 | 4173 | pc4HSA:HSA.2xBeta Defensin-2 | Pre-pro region of the HSA signal sequence followed by mature HSA fused to two tandem copies of Beta Defensin-2 at its C-terminus. | pC4 (Mammalian) | 523 | 487 | 559 | 592 | 593 | HSA |
| 104 | 4174 | pSAC35:ANP.HSA.BNP(S1-L29) | HSA/Kex-2 signal sequence followed by mature ANP fused to the N-terminus of mature HSA and BNP (amino acids 1-29) fused to the C-terminus of mature HSA. | pSAC35 | 524 | 488 | 560 | 594 | 595 | HSA/Kex-2 |
| 105 | 4175 | pc4HSA:HSA.beta Defensin-2 | Pre-pro region of the HSA signal sequence followed by mature HSA fused to beta Defensin-2 at its C-terminus. | pC4 (Mammalian) | 525 | 489 | 561 | 596 | 597 | HSA |
| 106 | 4176 | pc4HSA:HSASp.beta Defensin-2.HSA | Pre-pro region of the HSA signal sequence followed by beta Defensin-2 fused to the N-terminus of mature HSA. | pC4 (Mammalian) | 526 | 490 | 562 | 598 | 599 | HSA |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 107 | 4177 | pc4HSA:HSASp.2xbeta Defensin-2.HSA | Pre-pro region of the HSA signal sequence followed by two tandem copies of beta Defensin-2 fused to the N-terminus of mature HSA. | pC4 (Mammalian) | 527 | 491 | 563 | 600 | 601 | HSA |
| 108 | 4178 | pSAC35:KEX2.2xbetaDefensin-2.HSA | HSA/Kex-2 signal sequence followed by two tandem copies of beta Defensin-2 fused to the N-terminus of mature HSA. | pSAC35 | 528 | 492 | 564 | None | None | HSA/Kex-2 |
| 109 | 4179 | pSAC35:KEX2.beta Defensin-2.HSA | HSA/Kex-2 signal sequence followed by beta Defensin-2 fused to the N-terminus of mature HSA. | pSAC35 | 529 | 493 | 565 | None | None | HSA/Kex-2 |
| 110 | 4180 | pSAC35:HSA.beta Defensin-2 | HSA/Kex-2 signal sequence followed by mature HSA fused to beta defensin-2 at its C-terminus. | pSAC35 | 530 | 494 | 566 | None | None | HSA/Kex-2 |
| 111 | 4181 | pSAC35:HSA.2x.betaDefensin-2 | HSA/Kex-2 signal sequence followed by mature HSA fused to two tandem copies of beta Defensin-2 at its C-terminus. | pSAC35 | 531 | 495 | 567 | None | None | HSA/Kex-2 |
| 112 | 4191 | pSAC35:HSA.Fractalkine.Q25-G100 | HSA/Kex-2 signal sequence followed by mature HSA fused to soluble fractalkine (amino acids 25-100) at its C-terminus. | pSAC35 | 641 | 602 | 680 | None | None | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 113 | 4192 | pSAC35:Fractalkine. Q25-G100.HSA | HSA/Kex-2 signal sequence followed by soluble fractalkine (amino acids 25-100) fused to the N-terminus of mature HSA. | pSAC35 | 642 | 603 | 681 | None | None | HSA/Kex-2 |
| 114 | 4193 | pSAC35:Fractalkine. Q25-G100(R48Q).HSA | HSA/Kex-2 signal sequence followed by soluble mutant fractalkine (amino acids 25-100 (R48Q, corresponding to R71Q of full-length fractalkine)) fused to the N-terminus of mature HSA. | pSAC35 | 643 | 604 | 682 | None | None | HSA/Kex-2 |
| 115 | 4194 | pSAC35:Fractalkine. V29-G100.HSA | HSA/Kex-2 signal sequence followed by mature HSA fused to a soluble dominant negative form of fractalkine (amino acids 29-100) at its C-terminus. | pSAC35 | 644 | 605 | 683 | None | None | HSA/Kex-2 |
| 116 | 4213 | pSAC35:INVsp.OXM.HSA | Invertase signal sequence followed by full-length oxyntomodulin fused to the N-terminus of HSA. | pSAC35 | 645 | 606 | 684 | None | None | Invertase |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 117 | 4215 | pSAC35:INVsp.PYY 3-36.HSA(D25-E40).HSA.OXM | Invertase signal sequence followed by PYY (amino acids 3-36) fused via a 16 amino acid linker from HSA (amino acids 25-40) to the N-terminus of mature HSA which is fused at its C-terminus to full-length oxyntomodulin. | pSAC35 | 646 | 607 | 685 | 719 | 720 | Invertase |
| 118 | 4217 | pC4:HSA.OXM | Pre-pro region of the HSA signal sequence followed by mature HSA fused at its C-terminus to full-length oxyntomodulin. | pC4 (Mammalian) | 647 | 608 | 686 | 721 | 722 | HSA |
| 119 | 4227 | pSAC35:Invsp.KP.HSA(D25-E40).HSA | Invertase signal sequence followed by killer toxin peptide fused via a 16 amino acid linker from HSA (amino acids 25-40) to mature HSA. | pSAC35 | 648 | 609 | 687 | None | None | Invertase |
| 120 | 4232 | pCDNA3.1+: HSA.OXM | Pre-pro region of the HSA signal sequence followed by mature HSA fused at its C-terminus to full length oxyntomodulin. | pCDNA3.1+ | 649 | 610 | 688 | None | None | HSA |
| 121 | 4233 | pSAC35:KEX2.TIMP4.C30-G157.HSA | HSA/Kex-2 leader sequence followed by a C-terminal truncated form of mature TIMP4 (amino acids 30-157) fused to the N-terminus of mature HSA. | pSAC35 | 650 | 611 | 689 | 723 | 724 | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 122 | 4234 | pSAC35:HSA.TIMP.C30-G157 | HSA/Kex-2 leader sequence followed by mature HSA fused at its C-terminus to a C-terminal truncated form of mature TIMP4 (amino acids 30-157). | pSAC35 | 651 | 612 | 690 | 725 | 726 | HSA/Kex-2 |
| 123 | 4235 | pC4:HSA.2x(PYY 3-36) | Pre-pro region of the HSA signal sequence followed by mature HSA fused to two tandem copies of PYY (amino acids 3-36) at its C-terminus. | pC4 (Mammalian) | 652 | 613 | 691 | None | None | HSA |
| 124 | 4236 | pC4: SPCON2sp.PYY(3-36).HSA | A consensus signal sequence followed by PYY (amino acids 3-36) fused to the N-terminus of mature HSA. | pC4 (Mammalian) | 653 | 614 | 692 | 727 | None | Consensus |
| 125 | 4239 | pSAC35: [HSA/KEX(R19G)]sp.ADM.HSA | Modified HSA/Kex-2 leader sequence followed by adrenomedullin fused to the N-terminus of mature HSA. | pSAC35 | 654 | 615 | 693 | None | None | Modified HSA/Kex |
| 126 | 4240 | pC4: SPCON2sp.OXM.HSA | A consensus signal sequence followed by oxynotmodulin fused to the N-terminus of mature HSA. | pC4 (Mammalian) | 655 | 616 | 694 | None | None | Consensus |
| 127 | 4241 | pC4: HSA.Ghrelin | Pre-pro region of the HSA signal sequence followed by mature HSA fused to ghrelin at its C-terminus | pC4 (Mammalian) | 656 | 617 | 695 | 728 | 729 | HSA |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 128 | 4242 | pSAC35: HSA.Ghrelin | Pre-pro region of the HSA signal sequence followed by mature HSA fused to ghrelin at its C-terminus | pSAC35 | 657 | 618 | 696 | 730 | 731 | HSA |
| 129 | 4246 | pSAC35:CGRP(V8-F37).HSA | HSA/Kex-2 signal sequence followed by a truncated form of CGRP (amino acids 8-37) fused to the N-terminus of mature HSA. | pSAC35 | 658 | 619 | 697 | None | None | HSA/Kex-2 |
| 130 | 4247 | pSAC35:HSA.CGRP (V8-F37) | HSA/Kex-2 signal sequence followed by mature HSA fused to a truncated form of CGRP (amino acids 8-37) at its C-terminus. | pSAC35 | 659 | 620 | 698 | None | None | HSA/Kex-2 |
| 131 | 4248 | pSAC35:CGRP(L12-F37).HSA | HSA/Kex-2 signal sequence followed by a truncated form of CGRP (amino acids 12-37) fused to the N-terminus of mature HSA. | pSAC35 | 660 | 621 | 699 | None | None | HSA/Kex-2 |
| 132 | 4249 | pSAC35:HSA.CGRP (L12-F37) | HSA/Kex-2 signal sequence followed by a mature HSA fused to a truncated form of CGRP (amino acids 12-37) at its C-terminus. | pSAC35 | 661 | 622 | 700 | None | None | HSA/Kex-2 |
| 133 | 4251 | pSAC35:HSA.IGF1( G49-M153) | HSA/Kex-2 signal sequence followed by mature HSA fused to a mature form of IGF1 (amino acids 49-153) at its C-terminus. | pSAC35 | 662 | 623 | 701 | None | None | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 134 | 4252 | pSAC35:IGF1(G49-M153).HSA | HSA/Kex-2 signal sequence followed by a mature form of IGF1 (amino acids 49-153) fused to the N-terminus of mature HSA. | pSAC35 | 663 | 624 | 702 | None | None | HSA/Kex-2 |
| 135 | 4253 | pC4:SPCON2.OXM.OXM.HSA | A consensus signal sequence followed by two tandem copies of oxyntomodulin fused to the N-terminus of mature HSA. | pC4 (Mammalian) | 664 | 625 | 703 | None | None | Consensus |
| 136 | 4254 | pSAC35:NA(S35-K469).HSA | HSA/Kex-2 signal sequence followed an N-terminally truncated form of neuraminidase from Influenza A/Hong Kong/213/03 (HK213;H5N1) (amino acids 35-469) fused via a Gly-Ser linker (GGGGSGGGGSGG) to the N-terminus of mature HSA. | pSAC35 | 665 | 626 | 704 | None | None | HSA/Kex-2 |
| 137 | 4255 | pC4.SPCON2:NA(S35-K469).HSA | A consensus signal sequence followed by an N-terminally truncated form of neuraminidase from Influenza A/Hong Kong/213/03 (HK213;H5N1) (amino acids 35-469) fused via a Gly-Ser linker(GGGGSGGGGSGG) to the N-terminus of mature HSA. | pC4 (Mammalian) | 666 | 627 | 705 | None | None | Consensus |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 138 | 4256 | pSAC35:HA(D17-Q531).HSA | HSA/Kex-2 signal sequence followed by a truncated form of hemagglutinin from Influenza A/Hong Kong/213/03 (HK213;H5N1) (amino acids 17-531) lacking a signal peptide and the C-terminal hydrophobic domain, fused via a Gly-Ser linker (GGGGSGGGGSGG) to the N-terminus of mature HSA. | pSAC35 | 667 | 628 | 706 | None | None | HSA/Kex-2 |
| 139 | 4257 | pC4:SPCON2.HA(D17-Q531).HSA | A consensus signal sequence followed by a truncated form of hemagglutinin from Influenza A/Hong Kong/213/03 (HK213;H5N1) (amino acids 17-531) lacking a signal peptide and the C-terminal hydrophobic domain, fused via a Gly-Ser linker (GGGGSGGGGSGG) to the N-terminus of mature HSA. | pC4 (Mammalian) | 668 | 629 | 707 | None | None | Consensus |
| 140 | 4258 | pSAC35.BChE(E29-V557).HSA | HSA/Kex-2 signal sequence followed by butyrylcholinesterase (BChE) (amino acids 39-529 (A356W, Y360A, N45Q, N483Q, N509Q and N514Q)) fused to the N-terminus of mature HSA. | pSAC35 | 669 | 630 | 708 | None | None | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 141 | 4259 | pC4:SPCON2.BChE(E29-V557).HSA | A consensus signal sequence followed by butyrylcholinesterase (BChE) (amino acids 39-529 (A356W, Y360A, N45Q, N483Q, N509Q and N514Q)) fused to the N-terminus of mature HSA. | pC4 (Mammalian) | 670 | 631 | 709 | None | None | Consensus |
| 142 | 4260 | pC4:HSA.ADM (Y1-G53) | Pre-pro region of the HSA signal sequence followed by mature HSA fused at its C-terminus to adrenomedullin containing an additional glycine residue at the C-terminus (amino acids 1-53). | pC4 (Mammalian) | 671 | 632 | 710 | None | None | HSA |
| 143 | 4261 | pSAC35:HSA.ADM (Y1-G53) | HSA/Kex-2 signal sequence followed by mature HSA fused at its C-terminus to adrenomedullin containing an additional glycine residue at the C-terminus (amino acids 1-53). | pSAC35 | 672 | 633 | 711 | None | None | HSA/Kex-2 |
| 144 | 4262 | pC4:HSA.PYY(I3-G37) | Pre-pro region of the HSA signal sequence followed by mature HSA fused at its C-terminus to PYY containing an additional glycine residue at the C-terminus (amino acids 3-37). | pC4 (Mammalian) | 673 | 634 | 712 | None | None | HSA |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 145 | 4267 | pSAC35:HSA.PYY(I 3-G37) | HSA/Kex-2 signal sequence followed by mature HSA fused at its C-terminus to PYY containing an additional glycine residue at the C-terminus (amino acids 3-37). | pSAC35 | 674 | 635 | 713 | None | None | HSA/Kex-2 |
| 146 | 4290 | pSAC35:HSA(C34S) .INFa | HSA/Kex-2 signal sequence followed by a mutant mature HSA (C34S of mature HSA) fused to mature interferon alpha at its C-terminus. | pSAC35 | 675 | 636 | 714 | None | None | HSA/Kex-2 |
| 147 | 4291 | pSAC35.HSA.INFa( C586S) | HSA/Kex-2 signal sequence followed by mature HSA fused to a mutant mature interferon alpha (C1S of mature IFNa) at its C-terminus. | pSAC35 | 676 | 637 | 715 | None | None | HSA/Kex-2 |
| 148 | 4292 | pSAC35:HSA.INFa( C614S) | HSA/Kex-2 signal sequence followed by mature HSA fused to a mutant mature interferon alpha (C29S of mature IFNa) at its C-terminus. | pSAC35 | 677 | 638 | 716 | None | None | HSA/Kex-2 |
| 149 | 4295 | pSAC35:HSA.INFa( C683S) | HSA/Kex-2 signal sequence followed by mature HSA fused to a mutant mature interferon alpha (C98S of mature IFNa) at its C-terminus. | pSAC35 | 678 | 639 | 717 | None | None | HSA/Kex-2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 150 | 4296 | pSAC35:HSA.INFa(C723S) | HSA/Kex-2 signal sequence followed by mature HSA fused to a mutant mature interferon alpha (C138S of mature IFNa) at its C-terminus. | pSAC35 | 679 | 640 | 718 | None | None | HSA/Kex-2 |
| 151 | 3108 | pSAC35HSA.PYY | Mature PYY fused downstream of mature HSA and the HSA/kex2 leader. | pSAC35 | 744 | 732 | 756 | None | None | HSA/kex2 |
| 152 | 3109 | pSAC35HSA.PYY3-36 | HSA/kex2 leader followed by mature HSA and then PYY3-36 (SEQ ID NO:1799). | pSAC35 | 745 | 733 | 757 | None | None | HSA/kex2 |
| 153 | 3117 | pC4:PYY3-36/HSA | HSA leader followed by PYY3-36 (SEQ ID NO:1800) and mature HSA. | pC4 | 746 | 734 | 758 | 768 | 769 | HSA |
| 154 | 3118 | pSAC35:PYY3-36/HSA | HSA/kex2 leader followed by PYY3-36 (SEQ ID NO:1801) and mature HSA. | pSAC35 | 747 | 735 | 759 | 770 | 771 | HSA/kex2 |
| 155 | 3281 | pSAC35.PY3-36(x2)/HSA | PYY3-36 tandem repeat (x2) fused upstream of HSA and downstream of the HSA/kex2 signal peptide. | pSAC35 | 748 | 736 | 760 | 772 | 773 | HSA/kex2 |
| 156 | 3282 | pSAC35:HSA/PYY3-36(x2) | PYY3-36 tandem repeat (x2) fused downstream of mature HSA and HSA/kex2 leader. | pSAC35 | 749 | 737 | 761 | 774 | 775 | HSA/kex2 |

**Table 2**

| Fusion No. | Construct ID | Construct Name | Description | Expression Vector | SEQ ID NO: Y | SEQ ID NO: X | SEQ ID NO: Z | SEQ ID NO: A | SEQ ID NO: B | Leader Sequence |
|---|---|---|---|---|---|---|---|---|---|---|
| 157 | 3144 | pSAC35:adrenomedullin(27-52)/HSA | HSA/kex2 leader followed by amino acids 27-52 of adrenomedullin followed by mature HSA. | pSAC35 | 750 | 738 | 762 | 776 | 777 | HSA/kex2 |
| 158 | 3579 | pSAC35:HSA/kex2.HSA.oxyntomodulin | HSA/kex2 leader followed by mature HSA followed by mature oxyntomodulin. | pSAC35 | 751 | 739 | 763 | None | None | HSA/kex2 |
| 159 | 3580 | pSAC35:HSA/kex2.oxyntomodulin.HSA | HSA/kex2 leader followed by mature oxyntomodulin followed by mature HSA. | pSAC35 | 752 | 740 | 764 | None | None | HSA/kex2 |
| 160 | 4268 | pC4: SPCON2sp.Ghrelin.HSA | Consensus signal sequence followed by ghrelin fused to the N-terminus of HSA. | pC4 (Mammalian) | 753 | 741 | 765 | 778 | 779 | Consensus |
| 161 | 4273 | pSAC35:KEX2.TIMP4.C30-P224.HSA | HSA/Kex-2 signal sequence followed by mature TIMP4 (amino acids 30-224) fused to the N-terminus of mature HSA. | pSAC35 | 754 | 742 | 766 | None | None | HSA/Kex-2 |
| 162 | 4274 | pSAC35:HSA.TIMP4.C30-P224 | HSA/Kex-2 signal sequence followed by mature HSA fused to mature TIMP4 (amino acids 30-224) at its C-terminus. | pSAC35 | 755 | 743 | 767 | None | None | HSA/Kex-2 |

**[0089]** Table 2 provides a non-exhaustive list of polynucleotides of the invention comprising, or alternatively consisting of, nucleic acid molecules encoding an albumin fusion protein. The first column, "Fusion No." gives a fusion number to each polynucleotide. Column 2, "Construct ID" provides a unique numerical identifier for each polynucleotide of the invention. The Construct IDs may be used to identify polynucleotides which encode albumin fusion proteins comprising, or alternatively consisting of, a Therapeutic protein portion corresponding to a given Therapeutic Protein:X listed in the corresponding row of Table 1 wherein that Construct ID is listed in column 5. The "Construct Name" column (column 3) provides the name of a given albumin fusion construct or polynucleotide.

**[0090]** The fourth column in Table 2, "Description" provides a general description of a given albumin fusion construct, and the fifth column, "Expression Vector" lists the vector into which a polynucleotide comprising, or alternatively consisting of, a nucleic acid molecule encoding a given albumin fusion protein was cloned. Vectors are known in the art, and are available commercially or described elsewhere. For example, as described in the Examples, an "expression cassette" comprising, or alternatively consisting of, one or more of (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator, may be assembled in a convenient cloning vector and subsequently be moved into an alternative vector, such as, for example, an expression vector including, for example, a yeast expression vector or a mammalian expression vector. In one embodiment, for expression in *S. cervisiae*, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pSAC35. In another embodiment, for expression in CHO cells, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pC4. In a further embodiment, a polynucleotide comprising or alternatively consisting of a nucleic acid molecule encoding the Therapeutic protein portion of an albumin fusion protein is cloned into pC4:HSA. In a still further embodiment, for expression in NS0 cells, an expression cassette comprising, or alternatively consisting of, a nucleic acid molecule encoding an albumin fusion protein is cloned into pEE12. Other useful cloning and/or expression vectors will be known to the skilled artisan and are within the scope of the invention.

**[0091]** Column 6, "SEQ ID NO:Y," provides the full length amino acid sequence of the albumin fusion protein of the invention. In most instances, SEQ ID NO:Y shows the unprocessed form of the albumin fusion protein encoded – in other words, SEQ ID NO:Y shows the signal sequence, a HSA portion, and a therapeutic portion all encoded by the particular construct. Specifically

contemplated by the present invention are all polynucleotides that encode SEQ ID NO:Y. When these polynucleotides are used to express the encoded protein from a cell, the cell's natural secretion and processing steps produces a protein that lacks the signal sequence listed in columns 4 and/or 11 of Table 2. The specific amino acid sequence of the listed signal sequence is shown later in the specification or is well known in the art. Thus, most preferred embodiments of the present invention include the albumin fusion protein produced by a cell (which would lack the leader sequence shown in columns 4 and/or 11 of Table 2). Also most preferred are polypeptides comprising SEQ ID NO:Y without the specific leader sequence listed in columns 4 and/or 11 of Table 2. Compositions comprising these two preferred embodiments, including pharmaceutical compositions, are also preferred. Moreover, it is well within the ability of the skilled artisan to replace the signal sequence listed in columns 4 and/or 11 of Table 2 with a different signal sequence, such as those described later in the specification to facilitate secretion of the processed albumin fusion protein.

**[0092]** The seventh column, "SEQ ID NO:X," provides the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of a given albumin fusion protein may be derived. In one embodiment, the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of an albumin fusion protein may be derived comprises the wild type gene sequence encoding a Therapeutic protein shown in Table 1. In an alternative embodiment, the parent nucleic acid sequence from which a polynucleotide encoding a Therapeutic protein portion of an albumin fusion protein may be derived comprises a variant or derivative of a wild type gene sequence encoding a Therapeutic protein shown in Table 1, such as, for example, a synthetic codon optimized variant of a wild type gene sequence encoding a Therapeutic protein.

**[0093]** The eighth column, "SEQ ID NO:Z," provides a predicted translation of the parent nucleic acid sequence (SEQ ID NO:X). This parent sequence can be a full length parent protein used to derive the particular construct, the mature portion of a parent protein, a variant or fragment of a wildtype protein, or an artificial sequence that can be used to create the described construct. One of skill in the art can use this amino acid sequence shown in SEQ ID NO:Z to determine which amino acid residues of an albumin fusion protein encoded by a given construct are provided by the therapeutic protein. Moreover, it is well within the ability of the skilled artisan to use the sequence shown as SEQ ID NO:Z to derive the construct described in the same row. For example, if SEQ ID NO:Z corresponds to a full length protein, but only a portion of that protein is used to generate the specific CID, it is within the skill of the art to rely on molecular

biology techniques, such as PCR, to amplify the specific fragment and clone it into the appropriate vector.

**[0094]** Amplification primers provided in columns 9 and 10, "SEQ ID NO:A" and "SEQ ID NO:B" respectively, are exemplary primers used to generate a polynucleotide comprising or alternatively consisting of a nucleic acid molecule encoding the Therapeutic protein portion of a given albumin fusion protein. In one embodiment of the invention, oligonucleotide primers having the sequences shown in columns 9 and/or 10 (SEQ ID NOS:A and/or B) are used to PCR amplify a polynucleotide encoding the Therapeutic protein portion of an albumin fusion protein using a nucleic acid molecule comprising or alternatively consisting of the nucleotide sequence provided in column 7 (SEQ ID NO:X)of the corresponding row as the template DNA. PCR methods are well-established in the art. Additional useful primer sequences could readily be envisioned and utilized by those of ordinary skill in the art.

**[0095]** In an alternative embodiment, oligonucleotide primers may be used in overlapping PCR reactions to generate mutations within a template DNA sequence. PCR methods are known in the art.

**[0096]** As shown in Table 3, certain albumin fusion constructs disclosed in this application have been deposited with the ATCC®.

**Table 3**

| Construct ID | Construct Name | ATCC Deposit No./ Date |
|---|---|---|
| 2249 | pSAC35:IFNa2-HSA<br>also named pSAC23:IFNα2-HSA | PTA-3763<br>Oct. 4, 2001 |
| 2343 | pSAC35.INV-IFNA2.HSA | PTA-3940<br>Dec. 19, 2001 |
| 2381 | pC4:HSA-IFNa2(C17-E181) | PTA-3942<br>Dec. 19, 2001 |
| 2382 | pC4:IFNa2-HSA | PTA-3939<br>Dec. 19, 2001 |
| 3165 | pSAC35:HSA.IFNa<br>also named CID 3165, pSAC35:HSA.INFα | PTA-4670<br>Sept. 16, 2002 |

**[0097]** It is possible to retrieve a given albumin fusion construct from the deposit by techniques known in the art and described elsewhere herein (see, Example 10). The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

**[0098]** In a further embodiment of the invention, an "expression cassette" comprising, or

alternatively consisting of one or more of (1) a polynucleotide encoding a given albumin fusion protein, (2) a leader sequence, (3) a promoter region, and (4) a transcriptional terminator can be moved or "subcloned" from one vector into another. Fragments to be subcloned may be generated by methods well known in the art, such as, for example, PCR amplification (e.g., using oligonucleotide primers having the sequence shown in SEQ ID NO:A or B), and/or restriction enzyme digestion.

**[0099]** In preferred embodiments, the albumin fusion proteins of the invention are capable of a therapeutic activity and/or biologic activity corresponding to the therapeutic activity and/or biologic activity of the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein listed in the corresponding row of Table 1. In further preferred embodiments, the therapeutically active protein portions of the albumin fusion proteins of the invention are fragments or variants of the protein encoded by the sequence shown in SEQ ID NO:X column of Table 2, and are capable of the therapeutic activity and/or biologic activity of the corresponding Therapeutic protein.

***Polypeptide and Polynucleotide Fragments and Variants***

***Fragments***

**[00100]** The present invention is further directed to fragments of the Therapeutic proteins described in Table 1, albumin proteins, and/or albumin fusion proteins of the invention.

**[00101]** The present invention is also directed to polynucleotides encoding fragments of the Therapeutic proteins described in Table 1, albumin proteins, and/or albumin fusion proteins of the invention.

**[00102]** Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the Therapeutic protein, albumin protein, and/or albumin fusion protein of the invention, other Therapeutic activities and/or functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of polypeptides with N-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six

amino acid residues may often evoke an immune response.

**[00103]** Accordingly, fragments of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention, include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the reference polypeptide (i.e., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, N-terminal deletions may be described by the general formula m to q, where q is a whole integer representing the total number of amino acid residues in a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2), and m is defined as any integer ranging from 2 to q minus 6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[00104]** In addition, fragments of serum albumin polypeptides corresponding to an albumin protein portion of an albumin fusion protein of the invention, include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the reference polypeptide (i.e., serum albumin, or a serum albumin portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In preferred embodiments, N-terminal deletions may be described by the general formula m to 585, where 585 is a whole integer representing the total number of amino acid residues in mature human serum albumin (SEQ ID NO:1), and m is defined as any integer ranging from 2 to 579. Polynucleotides encoding these polypeptides are also encompassed by the invention. In additional embodiments, N-terminal deletions may be described by the general formula m to 609, where 609 is a whole integer representing the total number of amino acid residues in full length human serum albumin (SEQ ID NO:3), and m is defined as any integer ranging from 2 to 603. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[00105]** Moreover, fragments of albumin fusion proteins of the invention, include the full length albumin fusion protein as well as polypeptides having one or more residues deleted from the amino terminus of the albumin fusion protein (e.g., an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2; or an albumin fusion protein having the amino acid sequence disclosed in column 6 of Table 2). In particular, N-terminal deletions may be described by the general formula m to q, where q is a whole integer representing

the total number of amino acid residues in the albumin fusion protein, and m is defined as any integer ranging from 2 to q minus 6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[00106]** Also as mentioned above, even if deletion of one or more amino acids from the N-terminus or C-terminus of a reference polypeptide (e.g., a Therapeutic protein; serum albumin protein; or albumin fusion protein of the invention) results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) and/or Therapeutic activities may still be retained. For example the ability of polypeptides with C-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking the N-terminal and/or C-terminal residues of a reference polypeptide retains Therapeutic activity can readily be determined by routine methods described herein and/or otherwise known in the art.

**[00107]** The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to q minus 1, and where q is a whole integer representing the total number of amino acid residues in a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[00108]** In addition, the present invention provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of an albumin protein corresponding to an albumin protein portion of an albumin fusion protein of the invention (e.g., serum albumin or an albumin protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 2). In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to 584, where 584 is the whole integer representing the total number of amino acid residues in mature human serum albumin (SEQ ID NO:1) minus 1. Polynucleotides encoding

these polypeptides are also encompassed by the invention. In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to 608, where 608 is the whole integer representing the total number of amino acid residues in serum albumin (SEQ ID NO:3) minus 1. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0100]** Moreover, the present invention provides polypeptides having one or more residues deleted from the carboxy terminus of an albumin fusion protein of the invention. In particular, C-terminal deletions may be described by the general formula 1 to n, where n is any whole integer ranging from 6 to q minus 1, and where q is a whole integer representing the total number of amino acid residues in an albumin fusion protein of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0101]** In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted reference polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m to n of a reference polypeptide (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or serum albumin (e.g., SEQ ID NO:1), or an albumin protein portion of an albumin fusion protein of the invention, or an albumin protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or an albumin fusion protein, or an albumin fusion protein encoded by a polynucleotide or albumin fusion construct of the invention) where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0102]** The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a reference polypeptide sequence (e.g., a Therapeutic protein referred to in Table 1, or a Therapeutic protein portion of an albumin fusion protein of the invention, or a Therapeutic protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or serum albumin (e.g., SEQ ID NO: 1), or an albumin protein portion of an albumin fusion protein of the invention, or an albumin protein portion encoded by a polynucleotide or albumin fusion construct described in Table 2, or an albumin fusion protein, or an albumin fusion protein encoded by a polynucleotide or albumin fusion construct of the invention) set forth herein, or fragments thereof. In preferred embodiments, the application is directed to proteins comprising polypeptides at least 80%, 85%, 90%, 95%, 96%,

97%, 98% or 99% identical to reference polypeptides having the amino acid sequence of N- and C-terminal deletions as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0103]** Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a Therapeutic activity and/or functional activity (e.g. biological activity) of the polypeptide sequence of the Therapeutic protein or serum albumin protein of which the amino acid sequence is a fragment.

**[0104]** Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

***Variants***

**[0105]** "Variant" refers to a polynucleotide or nucleic acid differing from a reference nucleic acid or polypeptide, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the reference nucleic acid or polypeptide.

**[0106]** As used herein, "variant", refers to a Therapeutic protein portion of an albumin fusion protein of the invention, albumin portion of an albumin fusion protein of the invention, or albumin fusion protein of the invention differing in sequence from a Therapeutic protein (e.g. see "therapeutic" column of Table 1), albumin protein, and/or albumin fusion protein, respectively, but retaining at least one functional and/or therapeutic property thereof as described elsewhere herein or otherwise known in the art. Generally, variants are overall very similar, and, in many regions, identical to the amino acid sequence of the Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein, albumin protein corresponding to an albumin protein portion of an albumin fusion protein, and/or albumin fusion protein. Nucleic acids encoding these variants are also encompassed by the invention.

**[0107]** The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the amino acid sequence of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein of the invention (e.g., the amino acid sequence of a Therapeutic protein:X disclosed in Table 1; or the amino acid sequence of a Therapeutic protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 and 2, or fragments or variants thereof), albumin proteins corresponding to an albumin protein portion of an albumin fusion protein of the invention (e.g.,

the amino acid sequence of an albumin protein portion of an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 and 2; the amino acid sequence shown in SEQ ID NO: 1; or fragments or variants thereof), and/or albumin fusion proteins. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further polypeptides encompassed by the invention are polypeptides encoded by polynucleotides which hybridize to the complement of a nucleic acid molecule encoding an albumin fusion protein of the invention under stringent hybridization conditions (e.g., hybridization to filter bound DNA in 6X Sodium chloride/Sodium citrate (SSC) at about 45 degrees Celsius, followed by one or more washes in 0.2X SSC, 0.1% SDS at about 50 - 65 degrees Celsius), under highly stringent conditions (e.g., hybridization to filter bound DNA in 6X sodium chloride/Sodium citrate (SSC) at about 45 degrees Celsius, followed by one or more washes in 0.1X SSC, 0.2% SDS at about 68 degrees Celsius), or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds., 1989 *Current protocol in Molecular Biology*, Green publishing associates, Inc., and John Wiley & Sons Inc., New York, at pages 6.3.1 - 6.3.6 and 2.10.3). Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0108]** By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, or substituted with another amino acid. These alterations of the reference sequence may occur at the amino- or carboxy-terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

**[0109]** As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of an albumin fusion protein of the invention or a fragment thereof (such as a Therapeutic protein portion of the albumin fusion protein or an albumin portion of the albumin fusion protein), can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject

sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

**[0110]** If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

**[0111]** For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-

termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

**[0112]** The variant will usually have at least 75% (preferably at least about 80%, 90%, 95% or 99%) sequence identity with a length of normal HA or Therapeutic protein which is the same length as the variant. Homology or identity at the nucleotide or amino acid sequence level is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin *et al.*, Proc. Natl. Acad. Sci. USA 87: 2264-2268 (1990) and Altschul, J. Mol. Evol. 36: 290-300 (1993), fully incorporated by reference) which are tailored for sequence similarity searching.

**[0113]** The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see Altschul *et al.*, (Nature Genetics 6: 119-129 (1994)) which is fully incorporated by reference. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff *et al.*, Proc. Natl. Acad. Sci. USA 89: 10915-10919 (1992), fully incorporated by reference). For blastn, the scoring matrix is set by the ratios of M (i.e., the reward score for a pair of matching residues) to N (i.e., the penalty score for mismatching residues), wherein the default values for M and N are 5 and -4, respectively. Four blastn parameters may be adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every wink$^{th}$ position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent Blastp parameter settings were Q=9; R=2; wink=1; and gapw=32. A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty) and the equivalent settings in protein comparisons are GAP=8 and LEN=2.

**[0114]** The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing

alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host, such as, yeast or *E. coli*).

**[0115]** In a preferred embodiment, a polynucleotide of the invention which encodes the albumin portion of an albumin fusion protein is optimized for expression in yeast or mammalian cells. In a further preferred embodiment, a polynucleotide of the invention which encodes the Therapeutic protein portion of an albumin fusion protein is optimized for expression in yeast or mammalian cells. In a still further preferred embodiment, a polynucleotide encoding an albumin fusion protein of the invention is optimized for expression in yeast or mammalian cells.

**[0116]** In an alternative embodiment, a codon optimized polynucleotide which encodes a Therapeutic protein portion of an albumin fusion protein does not hybridize to the wild type polynucleotide encoding the Therapeutic protein under stringent hybridization conditions as described herein. In a further embodiment, a codon optimized polynucleotide which encodes an albumin portion of an albumin fusion protein does not hybridize to the wild type polynucleotide encoding the albumin protein under stringent hybridization conditions as described herein. In another embodiment, a codon optimized polynucleotide which encodes an albumin fusion protein does not hybridize to the wild type polynucleotide encoding the Therapeutic protein portion or the albumin protein portion under stringent hybridization conditions as described herein.

**[0117]** In an additional embodiment, a polynucleotide which encodes a Therapeutic protein portion of an albumin fusion protein does not comprise, or alternatively consist of, the naturally occurring sequence of that Therapeutic protein. In a further embodiment, a polynucleotide which encodes an albumin protein portion of an albumin fusion protein does not comprise, or alternatively consist of, the naturally occurring sequence of albumin protein. In an alternative embodiment, a polynucleotide which encodes an albumin fusion protein does not comprise, or alternatively consist of, the naturally occurring sequence of a Therapeutic protein portion or the albumin protein portion.

**[0118]** Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II,

Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

**[0119]** Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. As an example, Ron et al. (J. Biol. Chem. 268: 2984-2988 (1993)) reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

**[0120]** Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

**[0121]** Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

**[0122]** Thus, the invention further includes polypeptide variants which have a functional activity (e.g., biological activity and/or therapeutic activity). In one embodiment, the invention provides variants of albumin fusion proteins that have a functional activity (e.g., biological activity and/or

therapeutic activity) that corresponds to one or more biological and/or therapeutic activities of the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein. In another embodiment, the invention provides variants of albumin fusion proteins that have a functional activity (e.g., biological activity and/or therapeutic activity) that corresponds to one or more biological and/or therapeutic activities of the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. Polynucleotides encoding such variants are also encompassed by the invention.

**[0123]** In preferred embodiments, the variants of the invention have conservative substitutions. By "conservative substitutions" is intended swaps within groups such as replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

**[0124]** Guidance concerning how to make phenotypically silent amino acid substitutions is provided, for example, in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

**[0125]** The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

**[0126]** The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham and Wells, Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

**[0127]** As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) polypeptides containing substitutions of one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) polypeptides containing substitutions of one or more of the amino acid residues having a substituent group, or (iii) polypeptides which have been fused with or chemically conjugated to another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), (iv) polypeptide containing additional amino acids, such as, for example, an IgG Fc fusion region peptide. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

**[0128]** For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

**[0129]** In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of the amino acid sequence of an albumin fusion protein, the amino acid sequence of a Therapeutic protein and/or human serum albumin, wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Nucleic acids encoding these polypeptides are also encompassed by the invention.

**[0130]** The polypeptide of the present invention can be composed of amino acids joined to each

other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

***Functional activity***

**[0131]** "A polypeptide having functional activity" refers to a polypeptide capable of displaying one or more known functional activities associated with the full-length, pro-protein, and/or mature form of a Therapeutic protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

**[0132]** "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a Therapeutic protein of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

**[0133]** In preferred embodiments, an albumin fusion protein of the invention has at least one biological and/or therapeutic activity associated with the Therapeutic protein portion (or fragment or variant thereof) when it is not fused to albumin.

**[0134]** In additional preferred embodiments, the albumin fusion protein of the invention has an increased plasma stability compared to the Therapeutic protein portion (or fragment or variant thereof) in an unfused state. Plasma stability of the albumin fusion protein of the invention or of the unfused Therapeutic protein portion (or fragment or variant thereof) can be assayed using or routinely modifying assays known in the art.

**[0135]** The albumin fusion proteins of the invention can be assayed for functional activity (e.g., biological activity) using or routinely modifying assays known in the art, as well as assays described herein. Additionally, one of skill in the art may routinely assay fragments of a Therapeutic protein corresponding to a Therapeutic protein portion of an albumin fusion protein, for activity using assays referenced in its corresponding row of Table 1 (e.g., in column 3 of Table 1). Further, one of skill in the art may routinely assay fragments of an albumin protein corresponding to an albumin protein portion of an albumin fusion protein, for activity using assays known in the art and/or as described in the Examples section below.

**[0136]** For example, in one embodiment where one is assaying for the ability of an albumin fusion protein to bind or compete with a Therapeutic protein for binding to an anti-Therapeutic polypeptide antibody and/or anti-albumin antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel

agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

**[0137]** In a preferred embodiment, where a binding partner (e.g., a receptor or a ligand) of a Therapeutic protein is identified, binding to that binding partner by an albumin fusion protein which comprises that Therapeutic protein as the Therapeutic protein portion of the fusion can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of an albumin fusion protein to bind to a substrate(s) of the Therapeutic polypeptide corresponding to the Therapeutic protein portion of the fusion can be routinely assayed using techniques known in the art.

**[0138]** In an alternative embodiment, where the ability of an albumin fusion protein to multimerize is being evaluated, association with other components of the multimer can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., *supra.*

**[0139]** In preferred embodiments, an albumin fusion protein comprising all or a portion of an antibody that binds a Therapeutic protein, has at least one biological and/or therapeutic activity (e.g., to specifically bind a polypeptide or epitope) associated with the antibody that binds a Therapeutic protein (or fragment or variant thereof) when it is not fused to albumin. In other preferred embodiments, the biological activity and/or therapeutic activity of an albumin fusion protein comprising all or a portion of an antibody that binds a Therapeutic protein is the inhibition (i.e., antagonism) or activation (i.e., agonism) of one or more of the biological activities and/or therapeutic activities associated with the polypeptide that is specifically bound by antibody that binds a Therapeutic protein.

**[0140]** Albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be characterized in a variety of ways. In particular, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic

protein may be assayed for the ability to specifically bind to the same antigens specifically bound by the antibody that binds a Therapeutic protein corresponding to the Therapeutic protein portion of the albumin fusion protein using techniques described herein or routinely modifying techniques known in the art.

**[0141]** Assays for the ability of the albumin fusion proteins (e.g., comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to (specifically) bind a specific protein or epitope may be performed in solution (*e.g.*, Houghten, Bio/Techniques 13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Albumin fusion proteins comprising at least a fragment or variant of a Therapeutic antibody may also be assayed for their specificity and affinity for a specific protein or epitope using or routinely modifying techniques described herein or otherwise known in the art.

**[0142]** The albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for cross-reactivity with other antigens (e.g., molecules that have sequence/structure conservation with the molecule(s) specifically bound by the antibody that binds a Therapeutic protein (or fragment or variant thereof) corresponding to the Therapeutic protein portion of the albumin fusion protein of the invention) by any method known in the art.

**[0143]** Immunoassays which can be used to analyze (immunospecific) binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

**[0144]** Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis

buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding the albumin fusion protein of the invention (*e.g.*, comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding sepharose beads coupled to an anti-albumin antibody, for example, to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the albumin fusion protein to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the albumin fusion protein to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

**[0145]** Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), applying the albumin fusion protein of the invention (diluted in blocking buffer) to the membrane, washing the membrane in washing buffer, applying a secondary antibody (which recognizes the albumin fusion protein, *e.g.*, an anti-human serum albumin antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, $^{32}P$ or $^{125}I$) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

**[0146]** ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the albumin fusion protein (*e.g.*, comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) of the invention conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time,

washing away unbound or non-specifically bound albumin fusion proteins, and detecting the presence of the albumin fusion proteins specifically bound to the antigen coating the well. In ELISAs the albumin fusion protein does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes albumin fusion protein) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the albumin fusion protein may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

**[0147]** The binding affinity of an albumin fusion protein to a protein, antigen, or epitope and the off-rate of an albumin fusion protein-protein/antigen/epitope interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, $^{3}H$ or $^{125}I$) with the albumin fusion protein of the invention in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the albumin fusion protein for a specific protein, antigen, or epitope and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second protein that binds the same protein, antigen or epitope as the albumin fusion protein, can also be determined using radioimmunoassays. In this case, the protein, antigen or epitope is incubated with an albumin fusion protein conjugated to a labeled compound (*e.g.*, $^{3}H$ or $^{125}I$) in the presence of increasing amounts of an unlabeled second protein that binds the same protein, antigen, or epitope as the albumin fusion protein of the invention.

**[0148]** In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of albumin fusion proteins of the invention to a protein, antigen or epitope. BIAcore kinetic analysis comprises analyzing the binding and dissociation of albumin fusion proteins, or specific polypeptides, antigens or epitopes from chips with immobilized specific polypeptides, antigens or epitopes or albumin fusion proteins, respectively, on their surface.

**[0149]** Antibodies that bind a Therapeutic protein corresponding to the Therapeutic protein portion of an albumin fusion protein may also be described or specified in terms of their binding affinity for a given protein or antigen, preferably the antigen which they specifically bind.

Preferred binding affinities include those with a dissociation constant or Kd less than 5 X $10^{-2}$ M, $10^{-2}$ M, 5 X $10^{-3}$ M, $10^{-3}$ M, 5 X $10^{-4}$ M, $10^{-4}$ M. More preferred binding affinities include those with a dissociation constant or Kd less than 5 X $10^{-5}$ M, $10^{-5}$ M, 5 X $10^{-6}$ M, $10^{-6}$M, 5 X $10^{-7}$ M, $10^{7}$ M, 5 X $10^{-8}$ M or $10^{-8}$ M. Even more preferred binding affinities include those with a dissociation constant or Kd less than 5 X $10^{-9}$ M, $10^{-9}$ M, 5 X $10^{-10}$ M, $10^{-10}$ M, 5 X $10^{-11}$ M, $10^{-11}$ M, 5 X $10^{-12}$ M, $^{10-12}$ M, 5 X $10^{-13}$ M, $10^{-13}$ M, 5 X $10^{-14}$ M, $10^{-14}$ M, 5 X $10^{-15}$ M, or $10^{-15}$ M. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has an affinity for a given protein or epitope similar to that of the corresponding antibody (not fused to albumin) that binds a Therapeutic protein, taking into account the valency of the albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) and the valency of the corresponding antibody. In addition, assays described herein (see Examples and Table 1) and otherwise known in the art may routinely be applied to measure the ability of albumin fusion proteins and fragments, variants and derivatives thereof to elicit biological activity and/or Therapeutic activity (either *in vitro* or *in vivo*) related to either the Therapeutic protein portion and/or albumin portion of the albumin fusion protein. Other methods will be known to the skilled artisan and are within the scope of the invention.

***Albumin***

**[0150]** As described above, an albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion.

**[0151]** An additional embodiment comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are linked to one another by chemical conjugation.

**[0152]** The terms, human serum albumin (HSA) and human albumin (HA) are used interchangeably herein. The terms, "albumin and "serum albumin" are broader, and encompass human serum albumin (and fragments and variants thereof) as well as albumin from other species (and fragments and variants thereof).

**[0153]** As used herein, "albumin" refers collectively to albumin protein or amino acid sequence, or an albumin fragment or variant, having one or more functional activities (e.g., biological activities) of albumin. In particular, "albumin" refers to human albumin or fragments thereof (see for example, EP 201 239, EP 322 094 WO 97/24445, WO95/23857) especially the mature form of human albumin as shown in Figure 1 and SEQ ID NO: 1, or albumin from other vertebrates or

fragments thereof, or analogs or variants of these molecules or fragments thereof.

**[0154]** In preferred embodiments, the human serum albumin protein used in the albumin fusion proteins of the invention contains one or both of the following sets of point mutations with reference to SEQ ID NO: 1: Leu-407 to Ala, Leu-408 to Val, Val-409 to Ala, and Arg-410 to Ala; or Arg-410 to A, Lys-413 to Gln, and Lys-414 to Gln (see, e.g., International Publication No. WO95/23857, hereby incorporated in its entirety by reference herein). In even more preferred embodiments, albumin fusion proteins of the invention that contain one or both of above-described sets of point mutations have improved stability/resistance to yeast Yap3p proteolytic cleavage, allowing increased production of recombinant albumin fusion proteins expressed in yeast host cells.

**[0155]** As used herein, a portion of albumin sufficient to prolong the therapeutic activity or plasma stability or shelf-life of the Therapeutic protein refers to a portion of albumin sufficient in length or structure to stabilize or prolong the therapeutic activity or plasma stability of the protein so that the shelf life or plasma stability of the Therapeutic protein portion of the albumin fusion protein is prolonged or extended compared to the shelf-life or plasma stability in the non-fusion state. The albumin portion of the albumin fusion proteins may comprise the full length of the HA sequence as described above, or may include one or more fragments thereof that are capable of stabilizing or prolonging the therapeutic activity. Such fragments may be of 10 or more amino acids in length or may include about 15, 20, 25, 30, 50, or more contiguous amino acids from the HA sequence or may include part or all of specific domains of HA. For instance, one or more fragments of HA spanning the first two immunoglobulin-like domains may be used. In a preferred embodiment, the HA fragment is the mature form of HA.

**[0156]** The albumin portion of the albumin fusion proteins of the invention may be a variant of normal HA. The Therapeutic protein portion of the albumin fusion proteins of the invention may also be variants of the Therapeutic proteins as described herein. The term "variants" includes insertions, deletions and substitutions, either conservative or non conservative, where such changes do not substantially alter one or more of the oncotic, useful ligand-binding and non-immunogenic properties of albumin, or the active site, or active domain which confers the therapeutic activities of the Therapeutic proteins.

**[0157]** In particular, the albumin fusion proteins of the invention may include naturally occurring polymorphic variants of human albumin and fragments of human albumin, for example those fragments disclosed in EP 322 094 (namely HA (Pn), where n is 369 to 419). The albumin may be derived from any vertebrate, especially any mammal, for example human, cow, sheep, or pig.

Non-mammalian albumins include, but are not limited to, hen and salmon. The albumin portion of the albumin fusion protein may be from a different animal than the Therapeutic protein portion.

**[0158]** Generally speaking, an HA fragment or variant will be at least 100 amino acids long, preferably at least 150 amino acids long. The HA variant may consist of or alternatively comprise at least one whole domain of HA, for example domains 1 (amino acids 1-194 of SEQ ID NO: 1), domain 2 (amino acids 195-387 of SEQ ID NO:1), domain 3 (amino acids 388-585 of SEQ ID NO:1), domains 1 and 2 (1-387 of SEQ ID NO:1), domains 2 and 3 (195-585 of SEQ ID NO:1) or domains 1 and 3 (amino acids 1-194 of SEQ ID NO:1 and amino acids 388-585 of SEQ ID NO:1). Each domain is itself made up of two homologous subdomains namely 1-105, 120-194, 195-291, 316-387, 388-491 and 512-585, with flexible inter-subdomain linker regions comprising residues Lys106 to Glu119, Glu292 to Val315 and Glu492 to Ala511.

**[0159]** Preferably, the albumin portion of an albumin fusion protein of the invention comprises at least one subdomain or domain of HA or conservative modifications thereof. If the fusion is based on subdomains, some or all of the adjacent linker is preferably used to link to the Therapeutic protein moiety.

***Antibodies that Specifically bind Therapeutic proteins are also Therapeutic proteins***

**[0160]** The present invention also encompasses albumin fusion proteins that comprise at least a fragment or variant of an antibody that specifically binds a Therapeutic protein disclosed in Table 1. It is specifically contemplated that the term "Therapeutic protein" encompasses antibodies that bind a Therapeutic protein (e.g., as Described in column I of Table 1) and fragments and variants thereof. Thus an albumin fusion protein of the invention may contain at least a fragment or variant of a Therapeutic protein, and/or at least a fragment or variant of an antibody that binds a Therapeutic protein.

***Antibody structure and background***

**[0161]** The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. *See generally,*

*Fundamental Immunology* Chapters 3-5 (Paul, W., ed., 4th ed. Raven Press, N.Y. (1998)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site.

**[0162]** Thus, an intact IgG antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

**[0163]** The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDR regions, in general, are the portions of the antibody which make contact with the antigen and determine its specificity. The CDRs from the heavy and the light chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains variable regions comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The variable regions are connected to the heavy or light chain constant region. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J *Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

**[0164]** As used herein, "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds an antigen (e.g., a molecule containing one or more CDR regions of an antibody). Antibodies that may correspond to a Therapeutic protein portion of an albumin fusion protein include, but are not limited to, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies (e.g., single chain Fvs), Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies specific to antibodies of the invention), and epitope-binding fragments of any of the above (e.g., VH domains, VL domains, or one or more CDR regions).

***Antibodies that bind Therapeutic Proteins***

**[0165]** The present invention encompasses albumin fusion proteins that comprise at least a fragment or variant of an antibody that binds a Therapeutic Protein (e.g., as disclosed in Table 1) or fragment or variant thereof.

**[0166]** Antibodies that bind a Therapeutic protein (or fragment or variant thereof) may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (*e.g.*, mouse and rat), donkey, sheep, rabbit, goat, guinea pig, camel, horse, or chicken antibodies. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies

include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenomice or other organisms that have been genetically engineered to produce human antibodies.

**[0167]** The antibody molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the antibody molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG1. In other preferred embodiments, the immunoglobulin molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG2. In other preferred embodiments, the immunoglobulin molecules that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are IgG4.

**[0168]** Most preferably the antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains.

**[0169]** The antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a Therapeutic protein or may be specific for both a Therapeutic protein as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

**[0170]** Antibodies that bind a Therapeutic protein (or fragment or variant thereof) may be bispecific or bifunctional which means that the antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. *See, e.g.,* Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny et al. J

*Immunol.* 148:1547 1553 (1992). In addition, bispecific antibodies may be formed as "diabodies" (Holliger et al. "'Diabodies': small bivalent and bispecific antibody fragments" PNAS USA 90:6444-6448 (1993)) or "Janusins" (Traunecker et al. "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells" *EMBO J* 10:3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)).

**[0171]** The present invention also provides albumin fusion proteins that comprise, fragments or variants (including derivatives) of an antibody described herein or known elsewhere in the art. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues.

**[0172]** Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may be described or specified in terms of the epitope(s) or portion(s) of a Therapeutic protein which they recognize or specifically bind. Antibodies which specifically bind a Therapeutic protein or a specific epitope of a Therapeutic protein may also be excluded. Therefore, the present invention encompasses antibodies that specifically bind Therapeutic proteins, and allows for the exclusion of the same. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, binds the same epitopes as the unfused fragment or variant of that antibody itself.

**[0173]** Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a Therapeutic protein are included. Antibodies that bind polypeptides with at least 95%, at least

90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% sequence identity (as calculated using methods known in the art and described herein) to a Therapeutic protein are also included in the present invention. In specific embodiments, antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% sequence identity (as calculated using methods known in the art and described herein) to a Therapeutic protein are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has similar or substantially identical cross reactivity characteristics compared to the fragment or variant of that particular antibody itself.

**[0174]** Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide encoding a Therapeutic protein under stringent hybridization conditions (as described herein). Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than $5 \times 10^{-2}$ M, $10^{-2}$ M, $5 \times 10^{-3}$ M, $10^{-3}$ M, $5 \times 10^{-4}$ M, $10^{-4}$ M. More preferred binding affinities include those with a dissociation constant or Kd less than $5 \times 10^{-5}$ M, $10^{-5}$ M, $5 \times 10^{-6}$ M, $10^{-6}$M, $5 \times 10^{-7}$ M, $10^{7}$ M, $5 \times 10^{-8}$ M or $10^{-8}$ M. Even more preferred binding affinities include those with a dissociation constant or Kd less than $5 \times 10^{-9}$ M, $10^{-9}$ M, $5 \times 10^{-10}$ M, $10^{-10}$ M, $5 \times 10^{-11}$ M, $10^{-11}$ M, $5 \times 10^{-12}$ M, $^{10-12}$ M, $5 \times 10^{-13}$ M, $10^{-13}$ M, $5 \times 10^{-14}$ M, $10^{-14}$ M, $5 \times 10^{-15}$ M, or $10^{-15}$ M. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has an affinity for a given protein or epitope similar to that of the corresponding antibody (not fused to albumin) that binds a Therapeutic protein, taking into account the valency of the albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) and the valency of the corresponding antibody.

**[0175]** The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of a Therapeutic protein as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, competitively inhibits binding of a second antibody to an epitope of a Therapeutic protein. In other preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, competitively inhibits binding of a second antibody to an epitope of a Therapeutic protein by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

**[0176]** Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may act as agonists or antagonists of the Therapeutic protein. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody. In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, has similar or substantially similar characteristics with regard to preventing ligand binding and/or preventing receptor activation compared to an un-fused fragment or variant of the antibody that binds the Therapeutic protein.

**[0177]** The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent

binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the Therapeutic proteins (e.g. as disclosed in Table 1). The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties). In preferred embodiments, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, have similar or substantially identical agonist or antagonist properties as an un-fused fragment or variant of the antibody that binds the Therapeutic protein.

**[0178]** Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may be used, for example, to purify, detect, and target Therapeutic proteins, including both in *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the Therapeutic protein in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety. Likewise, albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, may be used, for example, to purify, detect, and target Therapeutic proteins, including both *in vitro* and *in vivo* diagnostic and therapeutic methods.

**[0179]** Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by

glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids. Albumin fusion proteins of the invention may also be modified as described above.

***Methods of Producing Antibodies that bind Therapeutic Proteins***

**[0180]** The antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a Therapeutic protein may be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

**[0181]** Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

**[0182]** Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art. In a non-limiting example, mice can be immunized with a Therapeutic protein or fragment or variant thereof, an albumin fusion protein, or a cell expressing such a Therapeutic protein or fragment or variant thereof or albumin fusion protein. Once an

immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

**[0183]** Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

**[0184]** Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

**[0185]** In general, the sample containing human B cells is innoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution

culture) or fused with a suitable fusion partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g, SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

**[0186]** Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

**[0187]** For example, antibodies that bind to a Therapeutic protein can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make antibodies that bind to a Therapeutic protein include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

**[0188]** As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human

antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

**[0189]** Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S.

Patent No. 5,565,332).

**[0190]** Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

**[0191]** Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181; and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide

human antibodies directed against a selected antigen using technology similar to that described above.

**[0192]** Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

***Polynucleotides Encoding Antibodies***

**[0193]** The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a Therapeutic protein, and more preferably, an antibody that binds to a polypeptide having the amino acid sequence of a "Therapeutic protein:X" as disclosed in the "SEQ ID NO:Z" column of Table 2.

**[0194]** The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

**[0195]** Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art (See Example 65).

**[0196]** Once the nucleotide sequence and corresponding amino acid sequence of the antibody is

determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties ), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

**[0197]** In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

**[0198]** In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

**[0199]** Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

***Recombinant Expression of Antibodies***

**[0200]** Recombinant expression of an antibody, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody or a single chain antibody), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

**[0201]** The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of

the entire immunoglobulin molecule, as detailed below.

**[0202]** A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

**[0203]** In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins

with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

**[0204]** In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

**[0205]** In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or *in vivo* recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

**[0206]** In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and

phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

**[0207]** For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

**[0208]** A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215 (1993)); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993);

Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

**[0209]** The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

**[0210]** Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

**[0211]** The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA

77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

**[0212]** Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

***Modifications of Antibodies***

**[0213]** Antibodies that bind a Therapeutic protein or fragments or variants can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin tag (also called the "HA tag"), which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

**[0214]** The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable

enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc. Other examples of detectable substances have been described elsewhere herein.

**[0215]** Further, an antibody of the invention may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

**[0216]** The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin;

or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

**[0217]** Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

**[0218]** Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

**[0219]** Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

**[0220]** An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

***Antibody-albumin fusion***

**[0221]** Antibodies that bind to a Therapeutic protein and that may correspond to a Therapeutic protein portion of an albumin fusion protein of the invention include, but are not limited to, antibodies that bind a Therapeutic protein disclosed in the "Therapeutic Protein X" column of Table 1, or a fragment or variant thereof.

**[0222]** In specific embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH domain. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or

alternatively consists of, one, two or three VH CDRs. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR1. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR2. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VH CDR3.

**[0223]** In specific embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL domain. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two or three VL CDRs. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR1. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR2. In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, the VL CDR3.

**[0224]** In other embodiments, the fragment or variant of an antibody that immunospecifcally binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, one, two, three, four, five, or six VH and/or VL CDRs.

**[0225]** In preferred embodiments, the fragment or variant of an antibody that immunospecifically binds a Therapeutic protein and that corresponds to a Therapeutic protein portion of an albumin fusion protein comprises, or alternatively consists of, an scFv comprising the VH domain of the Therapeutic antibody, linked to the VL domain of the therapeutic antibody by a peptide linker such as $(Gly_4Ser)_3$ (SEQ ID NO:4).

***Immunophenotyping***

**[0226]** The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may be utilized for immunophenotyping of cell lines and biological samples. Therapeutic proteins of the present invention may be useful as cell-specific markers, or more specifically as cellular markers that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies (or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies (or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

**[0227]** These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

***Characterizing Antibodies that bind a Therapeutic Protein and Albumin Fusion Proteins Comprising a Fragment or Variant of an Antibody that binds a Therapeutic Protein***

**[0228]** The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may be characterized in a variety of ways. In particular, Albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for the ability to specifically bind to the same antigens specifically bound by the antibody that binds a Therapeutic protein corresponding to the antibody that binds a Therapeutic protein portion of the albumin fusion protein using techniques described herein or routinely modifying techniques known in the art.

**[0229]** Assays for the ability of the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic

protein (or fragment or variant thereof) to (specifically) bind a specific protein or epitope may be performed in solution (*e.g.*, Houghten, Bio/Techniques 13:412-421(1992)), on beads (*e.g.*, Lam, Nature 354:82-84 (1991)), on chips (*e.g.*, Fodor, Nature 364:555-556 (1993)), on bacteria (*e.g.*, U.S. Patent No. 5,223,409), on spores (*e.g.*, Patent Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (*e.g.*, Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (*e.g.*, Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404-406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) may also be assayed for their specificity and affinity for a specific protein or epitope using or routinely modifying techniques described herein or otherwise known in the art.

**[0230]** The albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be assayed for cross-reactivity with other antigens (e.g., molecules that have sequence/structure conservation with the molecule(s) specifically bound by the antibody that binds a Therapeutic protein (or fragment or variant thereof) corresponding to the Therapeutic protein portion of the albumin fusion protein of the invention) by any method known in the art.

**[0231]** Immunoassays which can be used to analyze (immunospecific) binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

**[0232]** Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (*e.g.*, EDTA, PMSF, aprotinin, sodium vanadate), adding an antibody of the invention or albumin fusion protein of the invention comprising at least a

fragment or variant of an antibody that binds a Therapeutic protein (or fragment or variant thereof) to the cell lysate, incubating for a period of time (*e.g.*, 1 to 4 hours) at 40 degrees C, adding protein A and/or protein G sepharose beads (or beads coated with an appropriate anti-idiotypic antibody or anti-albumin antibody in the case when an albumin fusion protein comprising at least a fragment or variant of a Therapeutic antibody) to the cell lysate, incubating for about an hour or more at 40 degrees C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody or albumin fusion protein of the invention to immunoprecipitate a particular antigen can be assessed by, *e.g.*, western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody or albumin fusion protein to an antigen and decrease the background (*e.g.*, pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

**[0233]** Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (*e.g.*, 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (*e.g.*, PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (*e.g.*, PBS-Tween 20), applying the antibody or albumin fusion protein of the invention (diluted in blocking buffer) to the membrane, washing the membrane in washing buffer, applying a secondary antibody (which recognizes the albumin fusion protein, *e.g.*, an anti-human serum albumin antibody) conjugated to an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) or radioactive molecule (*e.g.*, $^{32}P$ or $^{125}I$) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

**[0234]** ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody or albumin fusion protein (comprising at least a fragment or variant of an antibody that binds a Therapeutic protein) of the invention conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of

time, washing away unbound or non-specifically bound albumin fusion proteins, and detecting the presence of the antibody or albumin fusion proteins specifically bound to the antigen coating the well. In ELISAs the antibody or albumin fusion protein does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody or albumin fusion protein, respectively) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, antibody or the albumin fusion protein may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (*e.g.*, horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, *e.g.*, Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

**[0235]** The binding affinity of an albumin fusion protein to a protein, antigen, or epitope and the off-rate of an antibody- or albumin fusion protein-protein/antigen/epitope interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (*e.g.*, $^{3}H$ or $^{125}I$) with the antibody or albumin fusion protein of the invention in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody or albumin fusion protein of the invention for a specific protein, antigen, or epitope and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second protein that binds the same protein, antigen or epitope as the antibody or albumin fusion protein, can also be determined using radioimmunoassays. In this case, the protein, antigen or epitope is incubated with an antibody or albumin fusion protein of the invention conjugated to a labeled compound (*e.g.*, $^{3}H$ or $^{125}I$) in the presence of increasing amounts of an unlabeled second protein that binds the same protein, antigen, or epitope as the albumin fusion protein of the invention.

**[0236]** In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibody or albumin fusion proteins of the invention to a protein, antigen or epitope. BIAcore kinetic analysis comprises analyzing the binding and dissociation of antibodies, albumin fusion proteins, or specific polypeptides, antigens or epitopes from chips with immobilized specific polypeptides, antigens or epitopes, antibodies or albumin fusion proteins, respectively, on their surface.

***Therapeutic Uses***

[0237] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein), nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein), albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein, and nucleic acids encoding such albumin fusion proteins. The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a Therapeutic protein, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a Therapeutic protein includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0238] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein to an animal, preferably a mammal, and most preferably a human, patient for treating one or more diseases, disorders, or conditions, including but not limited to: neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions., and/or as described elsewhere herein. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a Therapeutic protein and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or

prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a Therapeutic protein, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a Therapeutic protein includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

**[0239]** A summary of the ways in which the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be used therapeutically includes binding Therapeutic proteins locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein for diagnostic, monitoring or therapeutic purposes without undue experimentation.

**[0240]** The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

**[0241]** The antibodies of the invention or albumin fusion proteins of the invention comprising at least a fragment or variant of an antibody that binds a Therapeutic protein may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

**[0242]** It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against Therapeutic proteins, fragments or regions thereof, (or the albumin fusion protein correlate of such an antibody) for both immunoassays directed to and therapy of disorders

related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include dissociation constants or Kd's less than 5 X $10^{-2}$ M, $10^{-2}$ M, 5 X $10^{-3}$ M, $10^{-3}$ M, 5 X $10^{-4}$ M, $10^{-4}$ M. More preferred binding affinities include those with a dissociation constant or Kd less than 5 X $10^{-5}$ M, $10^{-5}$ M, 5 X $10^{-6}$ M, $10^{-6}$M, 5 X $10^{-7}$ M, $10^{7}$ M, 5 X $10^{-8}$ M or $10^{-8}$ M. Even more preferred binding affinities include those with a dissociation constant or Kd less than 5 X $10^{-9}$ M, $10^{-9}$ M, 5 X $10^{-10}$ M, $10^{-10}$ M, 5 X $10^{-11}$ M, $10^{-11}$ M, 5 X $10^{-12}$ M, $10^{-12}$ M, 5 X $10^{-13}$ M, $10^{-13}$ M, 5 X $10^{-14}$ M, $10^{-14}$ M, 5 X $10^{-15}$ M, or $10^{-15}$ M.

***Gene Therapy***

**[0243]** In a specific embodiment, nucleic acids comprising sequences encoding antibodies that bind therapeutic proteins or albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a Therapeutic protein, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

**[0244]** Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described in more detail elsewhere in this application.

***Demonstration of Therapeutic or Prophylactic Activity***

**[0245]** The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

***Therapeutic/Prophylactic Administration and Composition***

**[0246]** The invention provides methods of treatment, inhibition and prophylaxis by

administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

**[0247]** Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

**[0248]** Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

**[0249]** In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

**[0250]** In another embodiment, the compound or composition can be delivered in a vesicle, in

particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

**[0251]** In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

**[0252]** Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

**[0253]** In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

**[0254]** The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is

administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

**[0255]** In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

**[0256]** The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as

those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

**[0257]** The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a Therapeutic protein can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

**[0258]** For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

***Diagnosis and Imaging***

**[0259]** Labeled antibodies and derivatives and analogs thereof that bind a Therapeutic protein (or fragment or variant thereof) (including albumin fusion proteins comprising at least a fragment or variant of an antibody that binds a Therapeutic protein), can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of Therapeutic protein. The invention provides for the detection of aberrant expression of a Therapeutic protein, comprising (a) assaying the expression of the Therapeutic protein in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed Therapeutic protein expression level compared to the standard expression level is indicative of aberrant expression.

**[0260]** The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the Therapeutic protein in cells or body fluid of an individual using one or more antibodies specific to the Therapeutic protein or albumin fusion proteins comprising

at least a fragment of variant of an antibody specific to a Therapeutic protein, and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed Therapeutic protein gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

**[0261]** Antibodies of the invention or albumin fusion proteins comprising at least a fragment of variant of an antibody specific to a Therapeutic protein can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[0262]** One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a Therapeutic protein in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the Therapeutic protein is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the therapeutic protein. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

**[0263]** It will be understood in the art that the size of the subject and the imaging system used

will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody, antibody fragment, or albumin fusion protein comprising at least a fragment or variant of an antibody that binds a Therapeutic protein will then preferentially accumulate at the location of cells which contain the specific Therapeutic protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

**[0264]** Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

**[0265]** In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

**[0266]** Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

**[0267]** In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI). Antibodies that specifically detect the albumin fusion protein but not albumin or the therapeutic protein alone are a preferred embodiment. These can be used to detect the albumin fusion protein as described throughout the specification.

*Kits*

[0268] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0269] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0270] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0271] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting

means may include a labeled, competing antigen.

**[0272]** In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

**[0273]** The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

**[0274]** Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

***Albumin Fusion Proteins***

**[0275]** The present invention relates generally to albumin fusion proteins and methods of treating, preventing, or ameliorating diseases or disorders. As used herein, "albumin fusion protein" refers to a protein formed by the fusion of at least one molecule of albumin (or a fragment or variant thereof) to at least one molecule of a Therapeutic protein (or fragment or variant thereof). An albumin fusion protein of the invention comprises at least a fragment or variant of a Therapeutic protein and at least a fragment or variant of human serum albumin, which are associated with one another, preferably by genetic fusion (i.e., the albumin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a Therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of albumin) or to one another. The Therapeutic protein and albumin protein, once part of the albumin fusion protein, may each be referred to as a "portion", "region" or "moiety" of the albumin fusion protein.

**[0276]** In a preferred embodiment, the invention provides an albumin fusion protein encoded by a polynucleotide or albumin fusion construct described in Table 1 or Table 2. Polynucleotides encoding these albumin fusion proteins are also encompassed by the invention.

**[0277]** Preferred albumin fusion proteins of the invention, include, but are not limited to, albumin fusion proteins encoded by a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof); a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof) generated as described in Table 1, Table 2 or in the Examples; or a nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide encoding at least one molecule of albumin (or a fragment or variant thereof) joined in frame to at least one polynucleotide encoding at least one molecule of a Therapeutic protein (or fragment or variant thereof), further comprising, for example, one or more of the following elements: (1) a functional self-replicating vector (including but not limited to, a shuttle vector, an expression vector, an integration vector, and/or a replication system), (2) a region for initiation of transcription (e.g., a promoter region, such as for example, a regulatable or inducible promoter, a constitutive promoter), (3) a region for termination of transcription, (4) a leader sequence, and (5) a selectable marker.

**[0278]** In one embodiment, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein (e.g., as described in Table 1) and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a Therapeutic protein and a serum albumin protein. In other embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active variant of a Therapeutic protein and a serum albumin protein. In preferred embodiments, the serum albumin protein component of the albumin fusion protein is the mature portion of serum albumin.

**[0279]** In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein, and a biologically active and/or therapeutically active fragment of serum albumin. In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a Therapeutic protein and a biologically

active and/or therapeutically active variant of serum albumin. In preferred embodiments, the Therapeutic protein portion of the albumin fusion protein is the mature portion of the Therapeutic protein.

**[0280]** In further embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment or variant of a Therapeutic protein and a biologically active and/or therapeutically active fragment or variant of serum albumin. In preferred embodiments, the invention provides an albumin fusion protein comprising, or alternatively consisting of, the mature portion of a Therapeutic protein and the mature portion of serum albumin.

**[0281]** Preferably, the albumin fusion protein comprises HA as the N-terminal portion, and a Therapeutic protein as the C-terminal portion. Alternatively, an albumin fusion protein comprising HA as the C-terminal portion, and a Therapeutic protein as the N-terminal portion may also be used.

**[0282]** In other embodiments, the albumin fusion protein has a Therapeutic protein fused to both the N-terminus and the C-terminus of albumin. In a preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are the same Therapeutic proteins. In an alternative preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins. In another preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins which may be used to treat or prevent the same or a related disease, disorder, or condition (e.g. as listed in the "Preferred Indication Y" column of Table 1). In another preferred embodiment, the Therapeutic proteins fused at the N- and C- termini are different Therapeutic proteins which may be used to treat, ameliorate, or prevent diseases or disorders (e.g. as listed in the "Preferred Indication Y" column of Table 1) which are known in the art to commonly occur in patients simultaneously, concurrently, or consecutively, or which commonly occur in patients in association with one another.

**[0283]** Albumin fusion proteins of the invention encompass proteins containing one, two, three, four, or more molecules of a given Therapeutic protein X or variant thereof fused to the N- or C-terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof. Molecules of a given Therapeutic protein X or variants thereof may be in any number of orientations, including, but not limited to, a 'head to head' orientation (e.g., wherein the N-terminus of one molecule of a Therapeutic protein X is fused to the N-terminus of another molecule of the Therapeutic protein X), or a 'head to tail' orientation (e.g., wherein the C-terminus of one molecule of a Therapeutic protein X is fused to the N-terminus of another

molecule of Therapeutic protein X).

**[0284]** In one embodiment, one, two, three, or more tandemly oriented Therapeutic protein X polypeptides (or fragments or variants thereof) are fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof.

**[0285]** Albumin fusion proteins of the invention further encompass proteins containing one, two, three, four, or more molecules of a given Therapeutic protein X or variant thereof fused to the N- or C- terminus of an albumin fusion protein of the invention, and/or to the N- and/or C- terminus of albumin or variant thereof, wherein the molecules are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Albumin fusion proteins comprising multiple Therapeutic protein X polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology. Linkers are particularly important when fusing a small peptide to the large HSA molecule. The peptide itself can be a linker by fusing tandem copies of the peptide or other known linkers can be used. Constructs that incorporate linkers are described in Table 2 or are apparent when examining SEQ ID NO:Y.

**[0286]** Further, albumin fusion proteins of the invention may also be produced by fusing a Therapeutic protein X or variants thereof to the N-terminal and/or C-terminal of albumin or variants thereof in such a way as to allow the formation of intramolecular and/or intermolecular multimeric forms. In one embodiment of the invention, albumin fusion proteins may be in monomeric or multimeric forms (i.e., dimers, trimers, tetramers and higher multimers). In a further embodiment of the invention, the Therapeutic protein portion of an albumin fusion protein may be in monomeric form or multimeric form (i.e., dimers, trimers, tetramers and higher multimers). In a specific embodiment, the Therapeutic protein portion of an albumin fusion protein is in multimeric form (i.e., dimers, trimers, tetramers and higher multimers), and the albumin protein portion is in monomeric form.

**[0287]** In addition to albumin fusion protein in which the albumin portion is fused N- terminal and/or C-terminal of the Therapeutic protein portion, albumin fusion proteins of the invention may also be produced by inserting the Therapeutic protein or peptide of interest (e.g., a Therapeutic protein X as disclosed in Table 1, or an antibody that binds a Therapeutic protein or a fragment or variant thereof) into an internal region of HA. For instance, within the protein sequence of the HA molecule a number of loops or turns exist between the end and beginning of α-helices, which are stabilized by disulphide bonds. The loops, as determined from the crystal structure of HA (PDB identifiers 1AO6, 1BJ5, 1BKE, 1BM0, 1E7E to 1E7I and 1UOR) for the

most part extend away from the body of the molecule. These loops are useful for the insertion, or internal fusion, of therapeutically active peptides, particularly those requiring a secondary structure to be functional, or Therapeutic proteins, to essentially generate an albumin molecule with specific biological activity.

**[0288]** Loops in human albumin structure into which peptides or polypeptides may be inserted to generate albumin fusion proteins of the invention include: Val54-Asn61, Thr76-Asp89, Ala92-Glu100, Gln170-Ala176, His 247 - Glu252, Glu 266 - Glu277, Glu 280-His288, Ala362-Glu368, Lys439-Pro447, Val462-Lys475, Thr478-Pro486, and Lys560-Thr566. In more preferred embodiments, peptides or polypeptides are inserted into the Val54-Asn61, Gln170-Ala176, and/or Lys560-Thr566 loops of mature human albumin (SEQ ID NO:1).

**[0289]** Peptides to be inserted may be derived from either phage display or synthetic peptide libraries screened for specific biological activity or from the active portions of a molecule with the desired function. Additionally, random peptide libraries may be generated within particular loops or by insertions of randomized peptides into particular loops of the HA molecule and in which all possible combinations of amino acids are represented.

**[0290]** Such library(s) could be generated on HA or domain fragments of HA by one of the following methods:

randomized mutation of amino acids within one or more peptide loops of HA or HA domain fragments. Either one, more or all the residues within a loop could be mutated in this manner;

replacement of, or insertion into one or more loops of HA or HA domain fragments (*i.e.*, internal fusion) of a randomized peptide(s) of length $X_n$ (where X is an amino acid and n is the number of residues;

N-, C- or N- and C- terminal peptide/protein fusions in addition to (a) and/or (b).

**[0291]** The HA or HA domain fragment may also be made multifunctional by grafting the peptides derived from different screens of different loops against different targets into the same HA or HA domain fragment.

**[0292]** In preferred embodiments, peptides inserted into a loop of human serum albumin are peptide fragments or peptide variants of the Therapeutic proteins disclosed in Table 1. More particularly, the invention encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids in length inserted into a loop of human serum albumin. The invention also encompasses

albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids fused to the N-terminus of human serum albumin. The invention also encompasses albumin fusion proteins which comprise peptide fragments or peptide variants at least 7 at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least 40 amino acids fused to the C-terminus of human serum albumin. For example, short peptides described in Table 1 and 2 (e.g., Therapeutic Y) can be inserted into the albumin loops.

**[0293]** Generally, the albumin fusion proteins of the invention may have one HA-derived region and one Therapeutic protein-derived region. Multiple regions of each protein, however, may be used to make an albumin fusion protein of the invention. Similarly, more than one Therapeutic protein may be used to make an albumin fusion protein of the invention. For instance, a Therapeutic protein may be fused to both the N- and C-terminal ends of the HA. In such a configuration, the Therapeutic protein portions may be the same or different Therapeutic protein molecules. The structure of bifunctional albumin fusion proteins may be represented as: X-HA-Y or Y-HA-X.

**[0294]** For example, an anti-BLyS™ scFv-HA-IFNα-2b fusion may be prepared to modulate the immune response to IFNα-2b by anti-BLyS™ scFv. An alternative is making a bi (or even multi) functional dose of HA-fusions *e.g.* HA-IFNα-2b fusion mixed with HA-anti-BLyS™ scFv fusion or other HA-fusions in various ratio's depending on function, half-life etc.

**[0295]** Bi- or multi-functional albumin fusion proteins may also be prepared to target the Therapeutic protein portion of a fusion to a target organ or cell type via protein or peptide at the opposite terminus of HA.

**[0296]** As an alternative to the fusion of known therapeutic molecules, the peptides could be obtained by screening libraries constructed as fusions to the N-, C- or N- and C- termini of HA, or domain fragment of HA, of typically 6, 8, 12, 20 or 25 or $X_n$ (where X is an amino acid (aa) and n equals the number of residues) randomized amino acids, and in which all possible combinations of amino acids were represented. A particular advantage of this approach is that the peptides may be selected *in situ* on the HA molecule and the properties of the peptide would therefore be as selected for rather than, potentially, modified as might be the case for a peptide derived by any other method then being attached to HA.

**[0297]** Additionally, the albumin fusion proteins of the invention may include a linker peptide between the fused portions to provide greater physical separation between the moieties and thus

maximize the accessibility of the Therapeutic protein portion, for instance, for binding to its cognate receptor. The linker peptide may consist of amino acids such that it is flexible or more rigid.

**[0298]** The linker sequence may be cleavable by a protease or chemically to yield the growth hormone related moiety. Preferably, the protease is one which is produced naturally by the host, for example the *S. cerevisiae* protease *kex2* or equivalent proteases.

**[0299]** Therefore, as described above, the albumin fusion proteins of the invention may have the following formula R1-L-R2; R2-L-R1; or R1-L-R2-L-R1, wherein R1 is at least one Therapeutic protein, peptide or polypeptide sequence, and not necessarily the same Therapeutic protein, L is a linker and R2 is a serum albumin sequence.

**[0300]** In preferred embodiments, albumin fusion proteins of the invention comprising a Therapeutic protein have a higher plasma stability compared to the plasma stability of the same Therapeutic protein when not fused to albumin. Plasma stability typically refers to the time period between when the Therapeutic protein is administered in vivo and carried into the bloodstream and when the therapeutic protein is degraded and cleared from the bloodstream, into an organ, such as the kidney or liver, that ultimately clears the Therapeutic protein from the body. Plasma stability is calculated in terms of the half-life of the Therapeutic protein in the bloodstream. The half-life of the Therapeutic protein in the bloodstream can be readily determined by common assays known in the art.

**[0301]** In preferred embodiments, Albumin fusion proteins of the invention comprising a Therapeutic protein have extended shelf life compared to the shelf life the same Therapeutic protein when not fused to albumin. Shelf-life typically refers to the time period over which the therapeutic activity of a Therapeutic protein in solution or in some other storage formulation, is stable without undue loss of therapeutic activity. Many of the Therapeutic proteins are highly labile in their unfused state. As described below, the typical shelf-life of these Therapeutic proteins is markedly prolonged upon incorporation into the albumin fusion protein of the invention.

**[0302]** Albumin fusion proteins of the invention with "prolonged" or "extended" shelf-life exhibit greater therapeutic activity relative to a standard that has been subjected to the same storage and handling conditions. The standard may be the unfused full-length Therapeutic protein. When the Therapeutic protein portion of the albumin fusion protein is an analog, a variant, or is otherwise altered or does not include the complete sequence for that protein, the prolongation of therapeutic activity may alternatively be compared to the unfused equivalent of

that analog, variant, altered peptide or incomplete sequence. As an example, an albumin fusion protein of the invention may retain greater than about 100% of the therapeutic activity, or greater than about 105%, 110%, 120%, 130%, 150% or 200% of the therapeutic activity of a standard when subjected to the same storage and handling conditions as the standard when compared at a given time point.

**[0303]** Shelf-life may also be assessed in terms of therapeutic activity remaining after storage, normalized to therapeutic activity when storage began. Albumin fusion proteins of the invention with prolonged or extended shelf-life as exhibited by prolonged or extended therapeutic activity may retain greater than about 50% of the therapeutic activity, about 60%, 70%, 80%, or 90% or more of the therapeutic activity of the equivalent unfused Therapeutic protein when subjected to the same conditions.

***Expression of Fusion Proteins***

**[0304]** The albumin fusion proteins of the invention may be produced as recombinant molecules by secretion from yeast, a microorganism such as a bacterium, or a human or animal cell line. Preferably, the polypeptide is secreted from the host cells.

**[0305]** A particular embodiment of the invention comprises a DNA construct encoding a signal sequence effective for directing secretion in yeast, particularly a yeast-derived signal sequence (especially one which is homologous to the yeast host), and the fused molecule of the first aspect of the invention, there being no yeast-derived pro sequence between the signal and the mature polypeptide.

**[0306]** The *Saccharomyces cerevisiae* invertase signal is a preferred example of a yeast-derived signal sequence.

**[0307]** Conjugates of the kind prepared by Poznansky *et al.*, (FEBS Lett. 239:18 (1988)), in which separately-prepared polypeptides are joined by chemical cross-linking, are not contemplated.

**[0308]** The present invention also includes a cell, preferably a yeast cell transformed to express an albumin fusion protein of the invention. In addition to the transformed host cells themselves, the present invention also contemplates a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a monoclonal culture, in a nutrient medium. If the polypeptide is secreted, the medium will contain the polypeptide, with the cells, or without the cells if they have been filtered or centrifuged away. Many expression systems are known and may be used, including bacteria (for example *E. coli* and *Bacillus subtilis*), yeasts (for example *Saccharomyces cerevisiae*, *Kluyveromyces lactis* and *Pichia pastoris*, filamentous fungi (for

example *Aspergillus*), plant cells, animal cells and insect cells.

**[0309]** Preferred yeast strains to be used in the production of albumin fusion proteins are D88, DXY1 and BXP10. D88 [*leu2-3*, *leu2-122*, *can1*, *pra1*, *ubc4*] is a derivative of parent strain AH22*his*$^+$ (also known as DB1; see, e.g., Sleep *et al.* Biotechnology 8:42-46 (1990)). The strain contains a *leu2* mutation which allows for auxotropic selection of 2 micron-based plasmids that contain the LEU2 gene. D88 also exhibits a derepression of PRB1 in glucose excess. The PRB1 promoter is normally controlled by two checkpoints that monitor glucose levels and growth stage. The promoter is activated in wild type yeast upon glucose depletion and entry into stationary phase. Strain D88 exhibits the repression by glucose but maintains the induction upon entry into stationary phase. The PRA1 gene encodes a yeast vacuolar protease, YscA endoprotease A, that is localized in the ER. The UBC4 gene is in the ubiquitination pathway and is involved in targeting short lived and abnormal proteins for ubiquitin dependant degradation. Isolation of this ubc4 mutation was found to increase the copy number of an expression plasmid in the cell and cause an increased level of expression of a desired protein expressed from the plasmid (see, e.g., International Publication No. WO99/00504, hereby incorporated in its entirety by reference herein).

**[0310]** DXY1, a derivative of D88, has the following genotype: [*leu2-3*, *leu2-122*, *can1*, *pra1*, *ubc4*, *ura3::yap3*]. In addition to the mutations isolated in D88, this strain also has a knockout of the YAP3 protease. This protease causes cleavage of mostly di-basic residues (RR, RK, KR, KK) but can also promote cleavage at single basic residues in proteins. Isolation of this yap3 mutation resulted in higher levels of full length HSA production (see, e.g., U.S. Patent No. 5,965,386 and Kerry-Williams et al., Yeast 14:161-169 (1998), hereby incorporated in their entireties by reference herein).

**[0311]** BXP10 has the following genotype: *leu2-3*, *leu2-122*, *can1*, *pra1*, *ubc4*, *ura3*, *yap3::URA3*, *lys2*, *hsp150::LYS2*, *pmt1::URA3*. In addition to the mutations isolated in DXY1, this strain also has a knockout of the PMT1 gene and the HSP150 gene. The PMT1 gene is a member of the evolutionarily conserved family of dolichyl-phosphate-D-mannose protein O-mannosyltransferases (Pmts). The transmembrane topology of Pmt1p suggests that it is an integral membrane protein of the endoplasmic reticulum with a role in O-linked glycosylation. This mutation serves to reduce/eliminate O-linked glycosylation of HSA fusions (see, e.g., International Publication No. WO00/44772, hereby incorporated in its entirety by reference herein). Studies revealed that the Hsp150 protein is inefficiently separated from rHA by ion exchange chromatography. The mutation in the HSP150 gene removes a potential contaminant

that has proven difficult to remove by standard purification techniques. See, e.g., U.S. Patent No. 5,783,423, hereby incorporated in its entirety by reference herein.

**[0312]** The desired protein is produced in conventional ways, for example from a coding sequence inserted in the host chromosome or on a free plasmid. The yeasts are transformed with a coding sequence for the desired protein in any of the usual ways, for example electroporation. Methods for transformation of yeast by electroporation are disclosed in Becker & Guarente (1990) *Methods Enzymol.* 194, 182.

**[0313]** Successfully transformed cells, *i.e.*, cells that contain a DNA construct of the present invention, can be identified by well known techniques. For example, cells resulting from the introduction of an expression construct can be grown to produce the desired polypeptide. Cells can be harvested and lysed and their DNA content examined for the presence of the DNA using a method such as that described by Southern (1975) *J. Mol. Biol.* 98, 503 or Berent *et al.* (1985) *Biotech.* 3, 208. Alternatively, the presence of the protein in the supernatant can be detected using antibodies.

**[0314]** Useful yeast plasmid vectors include pRS403-406 and pRS413-416 and are generally available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers HIS3, 7RP1, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps).

**[0315]** Preferred vectors for making albumin fusion proteins for expression in yeast include pPPC0005, pScCHSA, pScNHSA, and pC4:HSA which are described in detail in Example 1. Figure 2 shows a map of the pPPC0005 plasmid that can be used as the base vector into which polynucleotides encoding Therapeutic proteins may be cloned to form HA-fusions. It contains a *PRB1 S. cerevisiae* promoter (PRB1p), a Fusion leader sequence (FL), DNA encoding HA (rHA) and an *ADH1 S. cerevisiae* terminator sequence. The sequence of the fusion leader sequence consists of the first 19 amino acids of the signal peptide of human serum albumin (SEQ ID NO:3) and the last five amino acids of the mating factor alpha 1 promoter (SLDKR, see EP-A-387 319 which is hereby incorporated by reference in its entirety).

**[0316]** The plasmids, pPPC0005, pScCHSA, pScNHSA, and pC4:HSA were deposited on April 11, 2001 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 and given accession numbers ATCC PTA-3278, PTA-3276, PTA-3279, and PTA-3277, respectively. Another vector useful for expressing an albumin fusion protein in yeast the pSAC35 vector which is described in Sleep *et al.*, BioTechnology 8:42 (1990) which is

hereby incorporated by reference in its entirety.

[0317] A yeast promoter that can be used to express the albumin fusion protein is the MET25 promoter. See, for example, Dominik Mumburg, Rolf Muller and Martin Funk. Nucleic Acids Research, 1994, Vol. 22, No. 25, pp. 5767-5768. The Met25 promoter is 383 bases long (bases –382 to –1) and the genes expressed by this promoter are also known as Met15, Met17, and YLR303W. A preferred embodiment uses the sequence below, where, at the 5' end of the sequence below, the Not 1 site used in the cloning is underlined and at the 3' end, the ATG start codon is underlined:

GCGGCCGCCGGATGCAAGGGTTCGAATCCCTTAGCTCTCATTATTTTTTGCTTTTTCT
CTTGAGGTCACATGATCGCAAAATGGCAAATGGCACGTGAAGCTGTCGATATTGGGG
AACTGTGGTGGTTGGCAAATGACTAATTAAGTTAGTCAAGGCGCCATCCTCATGAAA
ACTGTGTAACATAATAACCGAAGTGTCGAAAAGGTGGCACCTTGTCCAATTGAACAC
GCTCGATGAAAAAAATAAGATATATATAAGGTTAAGTAAAGCGTCTGTTAGAAAGG
AAGTTTTTCCTTTTTCTTGCTCTCTTGTCTTTTCATCTACTATTTCCTTCGTGTAATACA
GGGTCGTCAGATACATAGATACAATTCTATTACCCCCATCCATACAATG (SEQ ID NO:5)

[0318] Additional promoters that can be used to express the albumin fusion protein in yeast include the following:

a) the cbh1 promoter:

TCTAGAGTTGTGAAGTCGGTAATCCCGCTGTATAGTAATACGAGTCGCATCTA
AATACTCCGAAGCTGCTGCGAACCCGGAGAATCGAGATGTGCTGGAAAGCTT
CTAGCGAGCGGCTAAATTAGCATGAAAGGCTATGAGAAATTCTGGAGACGGC
TTGTTGAATCATGGCGTTCCATTCTTCGACAAGCAAAGCGTTCCGTCGCAGTA
GCAGGCACTCATTCCCGAAAAAACTCGGAGATTCCTAAGTAGCGATGGAACC
GGAATAATATAATAGGCAATACATTGAGTTGCCTCGACGGTTGCAATGCAGG
GGTACTGAGCTTGGACATAACTGTTCCGTACCCCACCTCTTCTCAACCTTTGG
CGTTTCCCTGATTCAGCGTACCCGTACAAGTCGTAATCACTATTAACCCAGAC
TGACCGGACGTGTTTTGCCCTTCATTTGGAGAAATAATGTCATTGCGATGTGT
AATTTGCCTGCTTGACCGACTGGGGCTGTTCGAAGCCCGAATGTAGGATTGTT
ATCCGAACTCTGCTCGTAGAGGCATGTTGTGAATCTGTGTCGGGCAGGACAC
GCCTCGAAGGTTCACGGCAAGGGAAACCACCGATAGCAGTGTCTAGTAGCAA
CCTGTAAAGCCGCAATGCAGCATCACTGGAAAATACAAACCAATGGCTAAAA
GTACATAAGTTAATGCCTAAAGAAGTCATATACCAGCGGCTAATAATTGTAC

AATCAAGTGGCTAAACGTACCGTAATTTGCCAACGGCTTGTGGGGTTGCAGA
AGCAACGGCAAAGCCCCACTTCCCCACGTTTGTTTCTTCACTCAGTCCAATCT
CAGCTGGTGATCCCCCAATTGGGTCGCTTGTTTGTTCCGGTGAAGTGAAAGAA
GACAGAGGTAAGAATGTCTGACTCGGAGCGTTTTGCATACAACCAAGGGCAG
TGATGGAAGACAGTGAAATGTTGACATTCAAGGAGTATTTAGCCAGGGATGC
TTGAGTGTATCGTGTAAGGAGGTTTGTCTGCCGATACGACGAATACTGTATAG
TCACTTCTGGTGAAGTGGTCCATATTGAAATGTAAGTCGGCACTGAACAGGCA
AAAGATTGAGTTGAAACTGCCTAAGATCTCGGGCCCTCGGGCCTTCGGCCTTT
GGGTGTACATGTTTGTGCTCCGGGCAAATGCAAAGTGTGGTAGGATCGAACA
CACTGCTGCCTTTACCAAGCAGCTGAGGGTATGTGATAGGCAAATGTTCAGG
GGCCACTGCATGGTTTCGAATAGAAAGAGAAGCTTAGCCAAGAACAATAGCC
GATAAAGATAGCCTCATTAAACGGAATGAGCTAGTAGGCAAAGTCAGCGAAT
GTGTATATATAAAGGTTCGAGGTCCGTGCCTCCCTCATGCTCTCCCCATCTAC
TCATCAACTCAGATCCTCCAGGAGACTTGTACACCATCTTTTGAGGCACAGAA
ACCCAATAGTCAACCGCGGACTGGCATC (SEQ ID NO:113)

b) the cysD promoter from *Aspergillus nidulans*:

AGATCTGGTTCCTGAGTACATCTACCGATGCGCCTCGATCCCCCTCTTAGCCGC
ATGAGATTCCTACCATTTATGTCCTATCGTTCAGGGTCCTATTTGGACCGCTAG
AAATAGACTCTGCTCGATTTGTTTCCATTATTCACGCAATTACGATAGTATTTG
GCTCTTTTCGTTTGGCCCAGGTCAATTCGGGTAAGACGCGATCACGCCATTGTG
GCCGCCGGCGTTGTGCTGCTGCTATTCCCCGCATATAAACAACCCCTCCACCA
GTTCGTTGGGCTTTGCGAATGCTGTACTCTATTTCAAGTTGTCAAAAGAGAGG
ATTCAAAAAATTATACCCCAGATATCAAAGATATCAAAGCCATC (SEQ ID
NO:114)

c) a modified cbh1 promoter having the sequence:

TCTAGAGTTGTGAAGTCGGTAATCCCGCTGTATAGTAATACGAGTCGCATCTA
AATACTCCGAAGCTGCTGCGAACCCGGAGAATCGAGATGTGCTGGAAAGCTT
CTAGCGAGCGGCTAAATTAGCATGAAAGGCTATGAGAAATTCTGGAGACGGC
TTGTTGAATCATGGCGTTCCATTCTTCGACAAGCAAAGCGTTCCGTCGCAGTA
GCAGGCACTCATTCCCGAAAAAACTCGGAGATTCCTAAGTAGCGATGGAACC
GGAATAATATAATAGGCAATACATTGAGTTGCCTCGACGGTTGCAATGCAGG
GGTACTGAGCTTGGACATAACTGTTCCGTACCCCACCTCTTCTCAACCTTTGG
CGTTTCCCTGATTCAGCGTACCCGTACAAGTCGTAATCACTATTAACCCAGAC

TGACCGGACGTGTTTTGCCCTTCATTTGGAGAAATAATGTCATTGCGATGTGT
AATTTGCCTGCTTGACCGACTGGGGCTGTTCGAAGCCCGAATGTAGGATTGTT
ATCCGAACTCTGCTCGTAGAGGCATGTTGTGAATCTGTGTCGGGCAGGACAC
GCCTCGAAGGTTCACGGCAAGGGAAACCACCGATAGCAGTGTCTAGTAGCAA
CCTGTAAAGCCGCAATGCAGCATCACTGGAAAATACAAACCAATGGCTAAAA
GTACATAAGTTAATGCCTAAAGAAGTCATATACCAGCGGCTAATAATTGTAC
AATCAAGTGGCTAAACGTACCGTAATTTGCCAACGGCTTGTGGGGTTGCAGA
AGCAACGGCAAAGCCCCACTTCCCCACGTTTGTTTCTTCACTCAGTCCAATCT
CAGCTGGTGATCCCCCAATTGGGTCGCTTGTTTGTTCCGGTGAAGTGAAAGAA
GACAGAGGTAAGAATGTCTGACTCGGAGCGTTTTGCATACAACCAAGGGCAG
TGATGGAAGACAGTGAAATGTTGACATTCAAGGAGTATTTAGCCAGGGATGC
TTGAGTGTATCGTGTAAGGAGGTTTGTCTGCCGATACGACGAATACTGTATAG
TCACTTCTGGTGAAGTGGTCCATATTGAAATGTAAGTCGGCACTGAACAGGCA
AAAGATTGAGTTGAAACTGCCTAAGATCTCGGGCCCTCGGGCCTTCGGCCTTT
GGGTGTACATGTTTGTGCTCCGGGCAAATGCAAAGTGTGGTAGGATCGAACA
CACTGCTGCCTTTACCAAGCAGCTGAGGGTATGTGATAGGCAAATGTTCAGG
GGCCACTGCATGGTTTCGAATAGAAAGAGAAGCTTAGCCTGCAGCCTCTTATC
GAGAAAGAAATTACCGTCGCTCGTGATTTGTTTGCAAAAAGAACAAAACTGA
AAAAACCCAGACACGCTCGACTTCCTGTCTTCCTATTGATTGCAGCTTCCAAT
TTCGTCACACAACAAGGTCCTAGCTTAGCCAAGAACAATAGCCGATAAAGAT
AGCCTCATTAAACGGAATGAGCTAGTAGGCAAAGTCAGCGAATGTGTATATA
TAAAGGTTCGAGGTCCGTGCCTCCCTCATGCTCTCCCCATCTACTCATCAACT
CAGATCCTCCAGGAGACTTGTACACCATCTTTTGAGGCACAGAAACCCAATA
GTCAACCGCGGACTGGCATC (SEQ ID NO:115)

d) a cysD promoter from *Aspergillus nidulans* having the sequence:

AGATCTGGTTCCTGAGTACATCTACCGATGCGCCTCGATCCCCCTCTTAGCCG
CATGAGATTCCTACCATTTATGTCCTATCGTTCAGGGTCCTATTTGGACCGCTA
GAAATAGACTCTGCTCGATTTGTTTCCATTATTCACGCAATTACGATAGTATTT
GGCTCTTTTCGTTTGGCCCAGGTCAATTCGGGTAAGACGCGATCACGCCATTG
TGGCCGCCGGCGCTGCAGCCTCTTATCGAGAAAGAAATTACCGTCGCTCGTG
ATTTGTTTGCAAAAAGAACAAAACTGAAAAAACCCAGACACGCTCGACTTCC
TGTCTTCCTATTGATTGCAGCTTCCAATTTCGTCACACAACAAGGTCCTACGC
CGGCGTTGTGCTGCTGCTATTCCCCGCATATAAACAACCCCTCCACCAGTTCG

TTGGGCTTTGCGAATGCTGTACTCTATTTCAAGTTGTCAAAAGAGAGGATTCA
AAAAATTATACCCCAGATATCAAAGATATCAAAGCCATC (SEQ ID NO:116)

**[0319]** A variety of methods have been developed to operably link DNA to vectors via complementary cohesive termini. For instance, complementary homopolymer tracts can be added to the DNA segment to be inserted to the vector DNA. The vector and DNA segment are then joined by hydrogen bonding between the complementary homopolymeric tails to form recombinant DNA molecules.

**[0320]** Synthetic linkers containing one or more restriction sites provide an alternative method of joining the DNA segment to vectors. The DNA segment, generated by endonuclease restriction digestion, is treated with bacteriophage T4 DNA polymerase or E. coli DNA polymerase I, enzymes that remove protruding, gamma-single-stranded termini with their 3' 5'-exonucleolytic activities, and fill in recessed 3'-ends with their polymerizing activities.

**[0321]** The combination of these activities therefore generates blunt-ended DNA segments. The blunt-ended segments are then incubated with a large molar excess of linker molecules in the presence of an enzyme that is able to catalyze the ligation of blunt-ended DNA molecules, such as bacteriophage T4 DNA ligase. Thus, the products of the reaction are DNA segments carrying polymeric linker sequences at their ends. These DNA segments are then cleaved with the appropriate restriction enzyme and ligated to an expression vector that has been cleaved with an enzyme that produces termini compatible with those of the DNA segment.

**[0322]** Synthetic linkers containing a variety of restriction endonuclease sites are commercially available from a number of sources including International Biotechnologies Inc, New Haven, CT, USA.

**[0323]** A desirable way to modify the DNA in accordance with the invention, if, for example, HA variants are to be prepared, is to use the polymerase chain reaction as disclosed by Saiki *et al.* (1988) *Science* 239, 487-491. In this method the DNA to be enzymatically amplified is flanked by two specific oligonucleotide primers which themselves become incorporated into the amplified DNA. The specific primers may contain restriction endonuclease recognition sites which can be used for cloning into expression vectors using methods known in the art.

**[0324]** Exemplary genera of yeast contemplated to be useful in the practice of the present invention as hosts for expressing the albumin fusion proteins are *Pichia* (Hansenula), *Saccharomyces, Kluyveromyces, Candida, Torulopsis, Torulaspora, Schizosaccharomyces, Citeromyces, Pachysolen, Debaromyces, Metschunikowia, Rhodosporidium, Leucosporidium, Botryoascus, Sporidiobolus, Endomycopsis*, and the like. Preferred genera are those selected from

the group consisting of *Saccharomyces, Schizosaccharomyces, Kluyveromyces, Pichia* and *Torulaspora.* Examples of *Saccharomyces spp.* are *S. cerevisiae, S. italicus and S. rouxii.*

**[0325]** Examples of Kluyveromyces spp. are K. fragilis, K. lactis and K. marxianus. A suitable Torulaspora species is T. delbrueckii. Examples of Pichia (Hansenula) spp. are P. angusta (formerly H. polymorpha), P. anomala (formerly H. anomala) and P. pastoris. Methods for the transformation of S. cerevisiae are taught generally in EP 251 744, EP 258 067 and WO 90/01063, all of which are incorporated herein by reference.

**[0326]** Preferred exemplary species of Saccharomyces include S. cerevisiae, S. italicus, S. diastaticus, and Zygosaccharomyces rouxii. Preferred exemplary species of Kluyveromyces include K. fragilis and K. lactis. Preferred exemplary species of Hansenula include H. polymorpha (now Pichia angusta), H. anomala (now Pichia anomala), and Pichia capsulata. Additional preferred exemplary species of Pichia include P. pastoris. Preferred exemplary species of Aspergillus include A. niger and A. nidulans. Preferred exemplary species of Yarrowia include Y. lipolytica. Many preferred yeast species are available from the ATCC. For example, the following preferred yeast species are available from the ATCC and are useful in the expression of albumin fusion proteins: Saccharomyces cerevisiae Hansen, teleomorph strain BY4743 yap3 mutant (ATCC Accession No. 4022731); Saccharomyces cerevisiae Hansen, teleomorph strain BY4743 hsp150 mutant (ATCC Accession No. 4021266); Saccharomyces cerevisiae Hansen, teleomorph strain BY4743 pmt1 mutant (ATCC Accession No. 4023792); Saccharomyces cerevisiae Hansen, teleomorph (ATCC Accession Nos. 20626; 44773; 44774; and 62995); Saccharomyces diastaticus Andrews et Gilliland ex van der Walt, teleomorph (ATCC Accession No. 62987); Kluyveromyces lactis (Dombrowski) van der Walt, teleomorph (ATCC Accession No. 76492); Pichia angusta (Teunisson et al.) Kurtzman, teleomorph deposited as Hansenula polymorpha de Morais et Maia, teleomorph (ATCC Accession No. 26012); Aspergillus niger van Tieghem, anamorph (ATCC Accession No. 9029); Aspergillus niger van Tieghem, anamorph (ATCC Accession No. 16404); Aspergillus nidulans (Eidam) Winter, anamorph (ATCC Accession No. 48756); and Yarrowia lipolytica (Wickerham et al.) van der Walt et von Arx, teleomorph (ATCC Accession No. 201847).

**[0327]** Suitable promoters for *S. cerevisiae* include those associated with the PGKI gene, GAL1 or GAL10 genes, CYCI, PHO5, TRPI, ADHI, ADH2, the genes for glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, triose phosphate isomerase, phosphoglucose isomerase, glucokinase, alpha-mating factor pheromone, [a mating factor pheromone], the PRBI promoter, the GUT2 promoter, the GPDI promoter, and hybrid

promoters involving hybrids of parts of 5' regulatory regions with parts of 5' regulatory regions of other promoters or with upstream activation sites (*e.g.* the promoter of EP-A-258 067).

**[0328]** Convenient regulatable promoters for use in *Schizosaccharomyces pombe* are the thiamine-repressible promoter from the nmt gene as described by Maundrell (1990) *J. Biol. Chem.* 265, 10857-10864 and the glucose repressible jbpl gene promoter as described by Hoffman & Winston (1990) *Genetics* 124, 807-816.

**[0329]** Methods of transforming *Pichia* for expression of foreign genes are taught in, for example, Cregg *et al.* (1993), and various Phillips patents (*e.g.* US 4 857 467, incorporated herein by reference), and *Pichia* expression kits are commercially available from Invitrogen BV, Leek, Netherlands, and Invitrogen Corp., San Diego, California. Suitable promoters include AOXI and AOX2. Gleeson *et al.* (1986) J. Gen. Microbiol. 132, 3459-3465 include information on *Hansenula* vectors and transformation, suitable promoters being MOX1 and FMD1; whilst EP 361 991, Fleer *et al.* (1991) and other- publications from Rhone-Poulenc Rorer teach how to express foreign proteins in *Kluyveromyces* spp., a suitable promoter being PGKI.

**[0330]** The transcription termination signal is preferably the 3' flanking sequence of a eukaryotic gene which contains proper signals for transcription termination and polyadenylation. Suitable 3' flanking sequences may, for example, be those of the gene naturally linked to the expression control sequence used, *i.e.* may correspond to the promoter. Alternatively, they may be different in which case the termination signal of the *S. cerevisiae* ADHI gene is preferred.

**[0331]** The desired albumin fusion protein may be initially expressed with a secretion leader sequence, which may be any leader effective in the yeast chosen. Leaders useful in yeast include any of the following:

a) the MPIF-1 signal sequence (e.g., amino acids 1-21 of GenBank Accession number AAB51134) MKVSVAALSCLMLVTALGSQA (SEQ ID NO:6)

b) the stanniocalcin signal sequence (MLQNSAVLLLLVISASA, SEQ ID NO:7)

c) the pre-pro region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYSRGVFRR, SEQ ID NO:8)

d) the pre region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYS, SEQ ID NO:9) or variants thereof, such as, for example, MKWVSFISLLFLFSSAYS, (SEQ ID NO:10)

e) the invertase signal sequence (e.g., MLLQAFLFLLAGFAAKISA, SEQ ID NO:11)

f) the yeast mating factor alpha signal sequence (e.g., MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPF

SNSTNNGLLFINTTIASIAAKEEGVSLEKR, SEQ ID NO:12 or MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPF SNSTNNGLLFINTTIASIAAKEEGVSLDKR, SEQ ID NO:12)

g) *K. lactis* killer toxin leader sequence

h) a hybrid signal sequence (e.g., MKWVSFISLLFLFSSAYSRSLEKR, SEQ ID NO:13)

i) an HSA/MFα-1 hybrid signal sequence (also known as HSA/kex2) (e.g., MKWVSFISLLFLFSSAYSRSLDKR, SEQ ID NO:14)

j) a *K. lactis* killer/ MFα-1 fusion leader sequence (e.g., MNIFYIFLFLLSFVQGSLDKR, SEQ ID NO:15)

k) the Immunoglobulin Ig signal sequence (e.g., MGWSCIILFLVATATGVHS, SEQ ID NO:16)

l) the Fibulin B precursor signal sequence (e.g., MERAAPSRRVPLPLLLLGGLALLAAGVDA, SEQ ID NO:17)

m) the clusterin precursor signal sequence (e.g., MMKTLLLFVGLLLTWESGQVLG, SEQ ID NO:18)

n) the insulin-like growth factor-binding protein 4 signal sequence (e.g., MLPLCLVAALLLAAGPGPSLG, SEQ ID NO:19)

o) variants of the pre-pro-region of the HSA signal sequence such as, for example, MKWVSFISLLFLFSSAYSRGVFRR (SEQ ID NO:20), MKWVTFISLLFLFAGVLG (SEQ ID NO:21), MKWVTFISLLFLFSGVLG (SEQ ID NO:22), MKWVTFISLLFLFGGVLG (SEQ ID NO:23), Modified HSA leader HSA #64 - MKWVTFISLLFLFAGVSG (SEQ ID NO:24); Modified HSA leader HSA #66 - MKWVTFISLLFLFGGVSG (SEQ ID NO:25); Modified HSA (A14) leader – MKWVTFISLLFLFAGVSG (SEQ ID NO:26); Modified HSA (S14) leader (also known as modified HSA #65) – MKWVTFISLLFLFSGVSG (SEQ ID NO:27), Modified HSA (G14) leader – MKWVTFISLLFLFGGVSG (SEQ ID NO:28), or MKWVTFISLLFLFGGVLGDLHKS (SEQ ID NO:29)

p) a consensus signal sequence (MPTWAWWLFLVLLLALWAPARG, SEQ ID NO:30)

q) acid phosphatase (PH05) leader (e.g., MFKSVVYSILAASLANA SEQ ID NO:31)

r) the pre-sequence of MFoz-1

s) the pre-sequence of 0 glucanase (BGL2)

t) killer toxin leader

u) the presequence of killer toxin

v) k. lactis killer toxin prepro (29 amino acids; 16 amino acids of pre and 13 amino acids of pro) MNIFYIFLFLLSFVQGLEHTHRRGSLDKR (SEQ ID NO:32)

w) *S. diastaticus* glucoamylase II secretion leader sequence

x) *S. carlsbergensis* β-galactosidase (MEL1) secretion leader sequence

y) *Candida glucoamylase* leader sequence

z) The hybrid leaders disclosed in EP-A-387 319 (herin incorporated by reference)

aa) the gp67 signal sequence (in conjunction with baculoviral expression systems) (e.g., amino acids 1-19 of GenBank Accession Number AAA72759) or

bb) the natural leader of the therapeutic protein X;

cc) S. cerevisiae invertase (SUC2) leader, as disclosed in JP 62-096086 (granted as 911036516, herein incorporate by reference); or

dd) Inulinase – MKLAYSLLLPLAGVSASVINYKR (SEQ ID NO:33).

ee) A modified TA57 propeptide leader variant #1 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLD VVGLISMAKR (SEQ ID NO:34)

ff) A modified TA57 propeptide leader variant #2 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLD VVGLISMAEEGEPKR (SEQ ID NO:35)

gg) A consensus signal peptide – MWWRLWWLLLLLLLLWPMVWA (SEQ ID NO:111)

hh) A modified HSA/kex2 signal sequence- MKWVSFISLLFLFSSAYSGSLDKR (SEQ ID NO:112)

ii) A consensus signal peptide #2 – MRPTWAWWLFLVLLLALWAPARG (SEQ ID NO:105)

***Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins***

**[0332]** The present invention also relates to vectors containing a polynucleotide encoding an albumin fusion protein of the present invention, host cells, and the production of albumin fusion proteins by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

**[0333]** The polynucleotides encoding albumin fusion proteins of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

**[0334]** The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac, trp, phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

**[0335]** As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418, glutamine synthase, or neomycin resistance for eukaryotic cell culture, and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli,* Streptomyces and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, NSO, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

**[0336]** Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

**[0337]** In one embodiment, polynucleotides encoding an albumin fusion protein of the invention

may be fused to signal sequences which will direct the localization of a protein of the invention to particular compartments of a prokaryotic or eukaryotic cell and/or direct the secretion of a protein of the invention from a prokaryotic or eukaryotic cell. For example, in *E. coli*, one may wish to direct the expression of the protein to the periplasmic space. Examples of signal sequences or proteins (or fragments thereof) to which the albumin fusion proteins of the invention may be fused in order to direct the expression of the polypeptide to the periplasmic space of bacteria include, but are not limited to, the *pelB* signal sequence, the maltose binding protein (MBP) signal sequence, MBP, the *ompA* signal sequence, the signal sequence of the periplasmic *E. coli* heat-labile enterotoxin B-subunit, and the signal sequence of alkaline phosphatase. Several vectors are commercially available for the construction of fusion proteins which will direct the localization of a protein, such as the pMAL series of vectors (particularly the pMAL-p series) available from New England Biolabs. In a specific embodiment, polynucleotides albumin fusion proteins of the invention may be fused to the *pelB* pectate lyase signal sequence to increase the efficiency of expression and purification of such polypeptides in Gram-negative bacteria. *See*, U.S. Patent Nos. 5,576,195 and 5,846,818, the contents of which are herein incorporated by reference in their entireties.

**[0338]** Examples of signal peptides that may be fused to an albumin fusion protein of the invention in order to direct its secretion in mammalian cells include, but are not limited to:

a) the MPIF-1 signal sequence (e.g., amino acids 1-21 of GenBank Accession number AAB51134) MKVSVAALSCLMLVTALGSQA (SEQ ID NO:6)
b) the stanniocalcin signal sequence (MLQNSAVLLLLVISASA, SEQ ID NO:7)
c) the pre-pro region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYSRGVFRR, SEQ ID NO:8)
d) the pre region of the HSA signal sequence (e.g., MKWVTFISLLFLFSSAYS, SEQ ID NO:9) or variants thereof, such as, for example, MKWVSFISLLFLFSSAYS, (SEQ ID NO:10)
e) the invertase signal sequence (e.g., MLLQAFLFLLAGFAAKISA, SEQ ID NO:11)
f) the yeast mating factor alpha signal sequence (e.g., MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPF SNSTNNGLLFINTTIASIAAKEEGVSLEKR, SEQ ID NO:12 or MRFPSIFTAVLAFAASSALAAPVNTTTEDETAQIPAEAVIGYSDLEGDFDVAVLPF SNSTNNGLLFINTTIASIAAKEEGVSLDKR, SEQ ID NO:12)
g) *K. lactis* killer toxin leader sequence

h) a hybrid signal sequence (e.g., MKWVSFISLLFLFSSAYSRSLEKR, SEQ ID NO:13)

i) an HSA/MFα-1 hybrid signal sequence (also known as HSA/kex2) (e.g., MKWVSFISLLFLFSSAYSRSLDKR, SEQ ID NO:14)

j) a *K. lactis* killer/ MFα-1 fusion leader sequence (e.g., MNIFYIFLFLLSFVQGSLDKR, SEQ ID NO:15)

k) the Immunoglobulin Ig signal sequence (e.g., MGWSCIILFLVATATGVHS, SEQ ID NO:16)

l) the Fibulin B precursor signal sequence (e.g., MERAAPSRRVPLPLLLLGGLALLAAGVDA, SEQ ID NO:17)

m) the clusterin precursor signal sequence (e.g., MMKTLLLFVGLLLTWESGQVLG, SEQ ID NO:18)

n) the insulin-like growth factor-binding protein 4 signal sequence (e.g., MLPLCLVAALLLAAGPGPSLG, SEQ ID NO:19)

o) variants of the pre-pro-region of the HSA signal sequence such as, for example, MKWVSFISLLFLFSSAYSRGVFRR (SEQ ID NO:20), MKWVTFISLLFLFAGVLG (SEQ ID NO:21), MKWVTFISLLFLFSGVLG (SEQ ID NO:22), MKWVTFISLLFLFGGVLG (SEQ ID NO:23), Modified HSA leader HSA #64 - MKWVTFISLLFLFAGVSG (SEQ ID NO:24); Modified HSA leader HSA #66 - MKWVTFISLLFLFGGVSG (SEQ ID NO:25); Modified HSA (A14) leader – MKWVTFISLLFLFAGVSG (SEQ ID NO:26); Modified HSA (S14) leader (also known as modified HSA #65) – MKWVTFISLLFLFSGVSG (SEQ ID NO:27), Modified HSA (G14) leader – MKWVTFISLLFLFGGVSG (SEQ ID NO:28), or MKWVTFISLLFLFGGVLGDLHKS (SEQ ID NO:29)

p) a consensus signal sequence (MPTWAWWLFLVLLLALWAPARG, SEQ ID NO:30)

q) acid phosphatase (PH05) leader (e.g., MFKSVVYSILAASLANA SEQ ID NO:31)

r) the pre-sequence of MFoz-1

s) the pre-sequence of 0 glucanase (BGL2)

t) killer toxin leader

u) the presequence of killer toxin

v) k. lactis killer toxin prepro (29 amino acids; 16 amino acids of pre and 13 amino acids of pro) MNIFYIFLFLLSFVQGLEHTHRRGSLDKR (SEQ ID NO:32)

w) *S. diastaticus* glucoarnylase II secretion leader sequence

x) *S. carlsbergensis* β-galactosidase (MEL1) secretion leader sequence

y) *Candida glucoarnylase* leader sequence

z) The hybrid leaders disclosed in EP-A-387 319 (herin incorporated by reference)

aa) the gp67 signal sequence (in conjunction with baculoviral expression systems) (e.g., amino acids 1-19 of GenBank Accession Number AAA72759) or

bb) the natural leader of the therapeutic protein X;

cc) S. cerevisiae invertase (SUC2) leader, as disclosed in JP 62-096086 (granted as 911036516, herein incorporate by reference); or

dd) Inulinase – MKLAYSLLLPLAGVSASVINYKR (SEQ ID NO:33).

ee) A modified TA57 propeptide leader variant #1 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLD VVGLISMAKR (SEQ ID NO:34)

ff) A modified TA57 propeptide leader variant #2 – MKLKTVRSAVLSSLFASQVLGQPIDDTESQTTSVNLMADDTESAFATQTNSGGLD VVGLISMAEEGEPKR (SEQ ID NO:35)

gg) A consensus signal peptide – MWWRLWWLLLLLLLLWPMVWA (SEQ ID NO:111)

jj) A modified HSA/kex2 signal sequence- MKWVSFISLLFLFSSAYSGSLDKR (SEQ ID NO:112)

kk) A consensus signal peptide #2 – MRPTWAWWLFLVLLLALWAPARG (SEQ ID NO:105)

**[0339]** In a preferred embodiment, the modified HSA/kex2 signal sequence (SEQ ID NO:112) is fused to the amino terminus of an albumin fusion protein, including fusion proteins comprising albumin and a therapeutic protein as described herein, as well as albumin fusion proteins disclosed in WO93/15199; WO97/24445; WO03/60071; WO03/59934; and PCT/US04/01369, each of which are incorporated herein by reference in their entireties. The modified HSA/kex2 signal sequence is based on the HSA/kex2 signal sequence (SEQ ID NO:14) disclosed, e.g., in Sleep et al., Biotechnology 1990, vol. 8, pp. 42-46; and US Patent 5,302,697, both of which are incorporated herein by reference in their entireties. The modified HSA/kex2 leader sequence disclosed herein contains a non-conservative amino acid substitution (Arg to Gly) at residue 19 of the parent signal peptide. The modified HSA/kex2 signal peptide has been found to produce unexpectedly better expression yield and/or better cleavage efficiency of albumin fusion proteins

when expressed in yeast than the unmodified HSA/kex2 signal sequence. Variants of the modified HSA/kex2 signal peptide are also encompassed by the invention. In particular the Gly residue at position 19 of SEQ ID NO:112 may be substituted with a Pro residue. Other conservative substitution variants of the modified HSA/kex2 signal sequence are also contemplated. Nucleic acids encoding the modified HSA/kex2 signal sequence of SEQ ID NO:112, as well as conservative substitution variants thereof, are also encompassed by the invention.

**[0340]** Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NSO) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

**[0341]** The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. A host strain may be chosen which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

**[0342]** Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

**[0343]** In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., the coding sequence corresponding to a Therapeutic protein may be replaced with an albumin fusion protein corresponding to the Therapeutic protein), and/or to include genetic material (e.g., heterologous polynucleotide sequences such as for example, an albumin fusion protein of the invention corresponding to the Therapeutic protein may be included). The genetic material operably associated with the endogenous polynucleotide may activate, alter, and/or amplify endogenous polynucleotides.

**[0344]** In addition, techniques known in the art may be used to operably associate heterologous polynucleotides (e.g., polynucleotides encoding an albumin protein, or a fragment or variant thereof) and/or heterologous control regions (e.g., promoter and/or enhancer) with endogenous polynucleotide sequences encoding a Therapeutic protein via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al., Proc. Natl. Acad. Sci. USA 86*:8932-8935 (1989); and Zijlstra *et al., Nature 342*:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

**[0345]** Albumin fusion proteins of the invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, hydrophobic charge interaction chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

**[0346]** In preferred embodiments the albumin fusion proteins of the invention are purified using Anion Exchange Chromatography including, but not limited to, chromatography on Q-sepharose, DEAE sepharose, poros HQ, poros DEAE, Toyopearl Q, Toyopearl QAE, Toyopearl DEAE,

Resource/Source Q and DEAE, Fractogel Q and DEAE columns.

**[0347]** In specific embodiments the albumin fusion proteins of the invention are purified using Cation Exchange Chromatography including, but not limited to, SP-sepharose, CM sepharose, poros HS, poros CM, Toyopearl SP, Toyopearl CM, Resource/Source S and CM, Fractogel S and CM columns and their equivalents and comparables.

**[0348]** In specific embodiments the albumin fusion proteins of the invention are purified using Hydrophobic Interaction Chromatography including, but not limited to, Phenyl, Butyl, Methyl, Octyl, Hexyl-sepharose, poros Phenyl, Butyl, Methyl, Octyl, Hexyl, Toyopearl Phenyl, Butyl, Methyl, Octyl, Hexyl Resource/Source Phenyl, Butyl, Methyl, Octyl, Hexyl, Fractogel Phenyl, Butyl, Methyl, Octyl, Hexyl columns and their equivalents and comparables.

**[0349]** In specific embodiments the albumin fusion proteins of the invention are purified using Size Exclusion Chromatography including, but not limited to, sepharose S100, S200, S300, superdex resin columns and their equivalents and comparables.

**[0350]** In specific embodiments the albumin fusion proteins of the invention are purified using Affinity Chromatography including, but not limited to, Mimetic Dye affinity, peptide affinity and antibody affinity columns that are selective for either the HSA or the "fusion target" molecules.

**[0351]** In preferred embodiments albumin fusion proteins of the invention are purified using one or more Chromatography methods listed above. In other preferred embodiments, albumin fusion proteins of the invention are purified using one or more of the following Chromatography columns, Q sepharose FF column, SP Sepharose FF column, Q Sepharose High Performance Column, Blue Sepharose FF column , Blue Column, Phenyl Sepharose FF column, DEAE Sepharose FF, or Methyl Column.

**[0352]** Additionally, albumin fusion proteins of the invention may be purified using the process described in PCT International Publication WO 00/44772 which is herein incorporated by reference in its entirety. One of skill in the art could easily modify the process described therein for use in the purification of albumin fusion proteins of the invention.

**[0353]** Albumin fusion proteins of the present invention may be recovered from: products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, albumin fusion proteins of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known

in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

**[0354]** In one embodiment, the yeast *Pichia pastoris* is used to express albumin fusion proteins of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using $O_2$. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for $O_2$. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

**[0355]** In one example, the plasmid vector pPIC9K is used to express DNA encoding an albumin fusion protein of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

**[0356]** Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

**[0357]** In another embodiment, high-level expression of a heterologous coding sequence, such as,

for example, a polynucleotide encoding an albumin fusion protein of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

**[0358]** In addition, albumin fusion proteins of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

**[0359]** The invention encompasses albumin fusion proteins of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

**[0360]** Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The albumin fusion proteins may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

**[0361]** Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine ($^{121}I$, $^{123}I$, $^{125}I$, $^{131}I$), carbon ($^{14}C$), sulfur ($^{35}S$), tritium ($^{3}H$), indium ($^{111}In$, $^{112}In$, $^{113m}In$, $^{115m}In$), technetium ($^{99}Tc$, $^{99m}Tc$), thallium ($^{201}Ti$), gallium ($^{68}Ga$, $^{67}Ga$), palladium ($^{103}Pd$), molybdenum ($^{99}Mo$), xenon ($^{133}Xe$), fluorine ($^{18}F$), $^{153}Sm$, $^{177}Lu$, $^{159}Gd$, $^{149}Pm$, $^{140}La$, $^{175}Yb$, $^{166}Ho$, $^{90}Y$, $^{47}Sc$, $^{186}Re$, $^{188}Re$, $^{142}Pr$, $^{105}Rh$, and $^{97}Ru$.

**[0362]** In specific embodiments, albumin fusion proteins of the present invention or fragments or variants thereof are attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, $^{177}Lu$, $^{90}Y$, $^{166}Ho$, and $^{153}Sm$, to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is $^{111}In$. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is $^{90}Y$. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al, Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

**[0363]** As mentioned, the albumin fusion proteins of the invention may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Polypeptides of the invention may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-

links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

**[0364]** Albumin fusion proteins of the invention and antibodies that bind a Therapeutic protein or fragments or variants thereof can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

**[0365]** Further, an albumin fusion protein of the invention may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin),

bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

**[0366]** The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors. Techniques for conjugating such therapeutic moiety to proteins (e.g., albumin fusion proteins) are well known in the art.

**[0367]** Albumin fusion proteins may also be attached to solid supports, which are particularly useful for immunoassays or purification of polypeptides that are bound by, that bind to, or associate with albumin fusion proteins of the invention. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

**[0368]** Albumin fusion proteins, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

**[0369]** In embodiments where the albumin fusion protein of the invention comprises only the VH domain of an antibody that binds a Therapeutic protein, it may be necessary and/or desirable to coexpress the fusion protein with the VL domain of the same antibody that binds a Therapeutic protein, such that the VH-albumin fusion protein and VL protein will associate (either covalently or non-covalently) post-translationally.

**[0370]** In embodiments where the albumin fusion protein of the invention comprises only the VL domain of an antibody that binds a Therapeutic protein, it may be necessary and/or desirable to coexpress the fusion protein with the VH domain of the same antibody that binds a Therapeutic

protein, such that the VL-albumin fusion protein and VH protein will associate (either covalently or non-covalently) post-translationally.

**[0371]** Some Therapeutic antibodies are bispecific antibodies, meaning the antibody that binds a Therapeutic protein is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. In order to create an albumin fusion protein corresponding to that Therapeutic protein, it is possible to create an albumin fusion protein which has an scFv fragment fused to both the N- and C- terminus of the albumin protein moiety. More particularly, the scFv fused to the N-terminus of albumin would correspond to one of the heavy/light (VH/VL) pairs of the original antibody that binds a Therapeutic protein and the scFv fused to the C-terminus of albumin would correspond to the other heavy/light (VH/VL) pair of the original antibody that binds a Therapeutic protein.

**[0372]** Also provided by the invention are chemically modified derivatives of the albumin fusion proteins of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The albumin fusion proteins may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

**[0373]** The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a Therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

**[0374]** As noted above, the polyethylene glycol may have a branched structure. Branched

polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

**[0375]** The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., Exp. Hematol. 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

**[0376]** As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

**[0377]** One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive

alkylation which exploits differential reactivity of different types of primary amino groups (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.

**[0378]** As indicated above, pegylation of the albumin fusion proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the albumin fusion protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

**[0379]** One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

**[0380]** Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

**[0381]** The number of polyethylene glycol moieties attached to each albumin fusion protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more

polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

**[0382]** The polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

**[0383]** The presence and quantity of albumin fusion proteins of the invention may be determined using ELISA, a well known immunoassay known in the art. In one ELISA protocol that would be useful for detecting/quantifying albumin fusion proteins of the invention, comprises the steps of coating an ELISA plate with an anti-human serum albumin antibody, blocking the plate to prevent non-specific binding, washing the ELISA plate, adding a solution containing the albumin fusion protein of the invention (at one or more different concentrations), adding a secondary anti-Therapeutic protein specific antibody coupled to a detectable label (as described herein or otherwise known in the art), and detecting the presence of the secondary antibody. In an alternate version of this protocol, the ELISA plate might be coated with the anti-Therapeutic protein specific antibody and the labeled secondary reagent might be the anti-human albumin specific antibody.

***Uses of the Polynucleotides***

**[0384]** Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

**[0385]** The polynucleotides of the present invention are useful to produce the albumin fusion proteins of the invention. As described in more detail below, polynucleotides of the invention (encoding albumin fusion proteins) may be used in recombinant DNA methods useful in genetic engineering to make cells, cell lines, or tissues that express the albumin fusion protein encoded by the polynucleotides encoding albumin fusion proteins of the invention.

**[0386]** Polynucleotides of the present invention are also useful in gene therapy. One goal of gene

therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the sections labeled "Gene Therapy", and Examples 61 and 62).

***Uses of the Polypeptides***

**[0387]** Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

**[0388]** Albumin fusion proteins of the invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

**[0389]** Albumin fusion proteins can be used to assay levels of polypeptides in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ($^{131}$I, $^{125}$I, $^{123}$I, $^{121}$I), carbon ($^{14}$C), sulfur ($^{35}$S), tritium ($^{3}$H), indium ($^{115m}$In, $^{113m}$In, $^{112}$In, $^{111}$In), and technetium ($^{99}$Tc, $^{99m}$Tc), thallium ($^{201}$Ti), gallium ($^{68}$Ga, $^{67}$Ga), palladium ($^{103}$Pd), molybdenum ($^{99}$Mo), xenon ($^{133}$Xe), fluorine ($^{18}$F), $^{153}$Sm, $^{177}$Lu, $^{159}$Gd, $^{149}$Pm, $^{140}$La, $^{175}$Yb, $^{166}$Ho, $^{90}$Y, $^{47}$Sc, $^{186}$Re, $^{188}$Re, $^{142}$Pr, $^{105}$Rh, $^{97}$Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[0390]** Albumin fusion proteins of the invention can also be detected *in vivo* by imaging. Labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, nuclear magnetic resonance (NMR) or electron spin relaxtion (ESR). For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the albumin fusion protein by labeling of nutrients given to a cell line expressing the albumin fusion protein of the invention.

**[0391]** An albumin fusion protein which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, $^{131}I$, $^{112}In$, $^{99m}Tc$, ($^{131}I$, $^{125}I$, $^{123}I$, $^{121}I$), carbon ($^{14}C$), sulfur ($^{35}S$), tritium ($^{3}H$), indium ($^{115m}In$, $^{113m}In$, $^{112}In$, $^{111}In$), and technetium ($^{99}Tc$, $^{99m}Tc$), thallium ($^{201}Ti$), gallium ($^{68}Ga$, $^{67}Ga$), palladium ($^{103}Pd$), molybdenum ($^{99}Mo$), xenon ($^{133}Xe$), fluorine ($^{18}F$, $^{153}Sm$, $^{177}Lu$, $^{159}Gd$, $^{149}Pm$, $^{140}La$, $^{175}Yb$, $^{166}Ho$, $^{90}Y$, $^{47}Sc$, $^{186}Re$, $^{188}Re$, $^{142}Pr$, $^{105}Rh$, $^{97}Ru$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99m}Tc$. The labeled albumin fusion protein will then preferentially accumulate at locations in the body (e.g., organs, cells, extracellular spaces or matrices) where one or more receptors, ligands or substrates (corresponding to that of the Therapeutic protein used to make the albumin fusion protein of the invention) are located. Alternatively, in the case where the albumin fusion protein comprises at least a fragment or variant of a Therapeutic antibody, the labeled albumin fusion protein will then preferentially accumulate at the locations in the body (e.g., organs, cells, extracellular spaces or matrices) where the polypeptides/epitopes corresponding to those bound by the Therapeutic antibody (used to make the albumin fusion protein of the invention) are located. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)). The protocols described therein could easily be modified by one of skill in the art for use with the albumin fusion proteins of the invention.

**[0392]** In one embodiment, the invention provides a method for the specific delivery of albumin fusion proteins of the invention to cells by administering albumin fusion proteins of the invention (e.g., polypeptides encoded by polynucleotides encoding albumin fusion proteins of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a Therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

**[0393]** In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering albumin fusion proteins of the invention in association with toxins or cytotoxic prodrugs.

**[0394]** By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, $^{213}$Bi, or other radioisotopes such as, for example, $^{103}$Pd, $^{133}$Xe, $^{131}$I, $^{68}$Ge, $^{57}$Co, $^{65}$Zn, $^{85}$Sr, $^{32}$P, $^{35}$S, $^{90}$Y, $^{153}$Sm, $^{153}$Gd, $^{169}$Yb, $^{51}$Cr, $^{54}$Mn, $^{75}$Se, $^{113}$Sn, $^{90}$Yttrium, $^{117}$Tin, $^{186}$Rhenium, $^{166}$Holmium, and $^{188}$Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin. In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope $^{90}$Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope $^{111}$In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope $^{131}$I.

**[0395]** Techniques known in the art may be applied to lable polypeptides of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274;119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

**[0396]** The albumin fusion proteins of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described herein under the section heading

"Biological Activities," below.

**[0397]** Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a certain polypeptide in cells or body fluid of an individual using an albumin fusion protein of the invention; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

**[0398]** Moreover, albumin fusion proteins of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

**[0399]** In particular, albumin fusion proteins comprising of at least a fragment or variant of a Therapeutic antibody can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an albumin fusion protein comprising of at least a fragment or variant of a Therapeutic antibody can bind, and/or neutralize the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds, and/or reduce overproduction of the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein specifically binds. Similarly, administration of an albumin fusion protein comprising of at least a fragment or variant of a Therapeutic antibody can activate the polypeptide to which the Therapeutic antibody used to make the albumin fusion protein

specifically binds, by binding to the polypeptide bound to a membrane (receptor).

**[0400]** At the very least, the albumin fusion proteins of the invention of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Albumin fusion proteins of the invention can also be used to raise antibodies, which in turn may be used to measure protein expression of the Therapeutic protein, albumin protein, and/or the albumin fusion protein of the invention from a recombinant cell, as a way of assessing transformation of the host cell, or in a biological sample. Moreover, the albumin fusion proteins of the present invention can be used to test the biological activities described herein.

***Diagnostic Assays***

**[0401]** The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, those described for each Therapeutic protein in the corresponding row of Table 1 and herein under the section headings "Immune Activity," "Blood Related Disorders," "Hyperproliferative Disorders," "Renal Disorders," "Cardiovascular Disorders," "Respiratory Disorders," "Anti-Angiogenesis Activity," "Diseases at the Cellular Level," "Wound Healing and Epithelial Cell Proliferation," "Neural Activity and Neurological Diseases," "Endocrine Disorders," "Reproductive System Disorders," "Infectious Disease," "Regeneration," and/or "Gastrointestinal Disorders," *infra.*

**[0402]** For a number of disorders, substantially altered (increased or decreased) levels of gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, that is, the expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding a polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

**[0403]** The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed gene expression will experience a worse clinical outcome.

**[0404]** By "assaying the expression level of the gene encoding a polypeptide" is intended

qualitatively or quantitatively measuring or estimating the level of a particular polypeptide (e.g. a polypeptide corresponding to a Therapeutic protein disclosed in Table 1) or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

**[0405]** By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing polypeptides of the invention (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a polypeptide or mRNA. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

**[0406]** Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the polypeptides of the invention are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

**[0407]** The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of polypeptides that bind to, are bound by, or associate with albumin fusion proteins of the invention, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting abnormal expression of polypeptides that bind to, are bound by, or associate with albumin fusion proteins compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide that bind to, are bound by, or associate with albumin fusion

proteins of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying polypeptide levels in a biological sample can occur using any art-known method.

**[0408]** Assaying polypeptide levels in a biological sample can occur using a variety of techniques. For example, polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other methods useful for detecting polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ($^{125}I$, $^{121}I$), carbon ($^{14}C$), sulfur ($^{35}S$), tritium ($^{3}H$), indium ($^{112}In$), and technetium ($^{99m}Tc$), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[0409]** The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the gene of interest (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the gene.

**[0410]** For example, albumin fusion proteins may be used to quantitatively or qualitatively detect the presence of polypeptides that bind to, are bound by, or associate with albumin fusion proteins of the present invention. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled albumin fusion protein coupled with light microscopic, flow cytometric, or fluorimetric detection.

**[0411]** In a preferred embodiment, albumin fusion proteins comprising at least a fragment or variant of an antibody that specifically binds at least a Therapeutic protein disclosed herein (e.g., the Therapeutic proteins disclosed in Table 1) or otherwise known in the art may be used to quantitatively or qualitatively detect the presence of gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow

cytometric, or fluorimetric detection.

**[0412]** The albumin fusion proteins of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of polypeptides that bind to, are bound by, or associate with an albumin fusion protein of the present invention. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or polypeptide of the present invention. The albumin fusion proteins are preferably applied by overlaying the labeled albumin fusion proteins onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the polypeptides that bind to, are bound by, or associate with albumin fusion proteins, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

**[0413]** Immunoassays and non-immunoassays that detect polypeptides that bind to, are bound by, or associate with albumin fusion proteins will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

**[0414]** The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled albumin fusion protein of the invention. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

**[0415]** By "solid phase support or carrier" is intended any support capable of binding a polypeptide (e.g., an albumin fusion protein, or polypeptide that binds, is bound by, or associates with an albumin fusion protein of the invention.) Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule

is capable of binding to a polypeptide. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

**[0416]** The binding activity of a given lot of albumin fusion protein may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

**[0417]** In addition to assaying polypeptide levels in a biological sample obtained from an individual, polypeptide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, albumin fusion proteins of the invention are used to image diseased or neoplastic cells.

**[0418]** Labels or markers for *in vivo* imaging of albumin fusion proteins of the invention include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the albumin fusion protein by labeling of nutrients of a cell line (or bacterial or yeast strain) engineered.

**[0419]** Additionally, albumin fusion proteins of the invention whose presence can be detected, can be administered. For example, albumin fusion proteins of the invention labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further, such polypeptides can be utilized for *in vitro* diagnostic procedures.

**[0420]** A polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, $^{131}I$, $^{112}In$, $^{99m}Tc$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99m}Tc$. The labeled albumin fusion protein will then preferentially accumulate at the locations in the body which contain a polypeptide or other substance that binds to, is bound by or associates with an albumin fusion protein of the present

invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

**[0421]** One of the ways in which an albumin fusion protein of the present invention can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

**[0422]** Albumin fusion proteins may also be radiolabelled and used in any of a variety of other immunoassays. For example, by radioactively labeling the albumin fusion proteins, it is possible to the use the albumin fusion proteins in a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

**[0423]** Additionally, chelator molecules, are known in the art and can be used to label the Albumin fusion proteins. Chelator molecules may be attached Albumin fusion proteins of the invention to facilitate labeling said protein with metal ions including radionuclides or fluorescent labels. For example, see Subramanian, R. and Meares, C.F., "Bifunctional Chelating Agents for

Radiometal-labeled monoclonal Antibodies," in *Cancer Imaging with Radiolabeled Antibodies* (D. M. Goldenberg, Ed.) Kluwer Academic Publications, Boston; Saji, H., "Targeted delivery of radiolabeled imaging and therapeutic agents: bifunctional radiopharmaceuticals." *Crit. Rev. Ther. Drug Carrier Syst. 16*:209-244 (1999); Srivastava S.C. and Mease R.C., "Progress in research on ligands, nuclides and techniques for labeling monoclonal antibodies." *Int. J. Rad. Appl. Instrum. B 18*:589-603 (1991); and Liu, S. and Edwards, D.S., "Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals." *Bioconjug. Chem. 12*:7-34 (2001). Any chelator which can be covalently bound to said Albumin fusion proteins may be used according to the present invention. The chelator may further comprise a linker moiety that connects the chelating moiety to the Albumin fusion protein.

**[0424]** In one embodiment, the Albumin fusion protein of the invention are attached to an acyclic chelator such as diethylene triamine-N,N,N',N",N"-pentaacetic acid (DPTA), analogues of DPTA, and derivatives of DPTA. As non-limiting examples, the chelator may be 2-(p-isothiocyanatobenzyl)-6- methyldiethylenetriaminepentaacetic acid (1B4M-DPTA, also known as MX-DTPA), 2-methyl-6-(rho-nitrobenzyl)-1,4,7- triazaheptane-N,N,N',N",N"-pentaacetic acid (nitro-1B4M-DTPA or nitro-MX-DTPA); 2-(p-isothiocyanatobenzyl)-cyclohexyldiethylenetriaminepentaacetic acid (CHX-DTPA), or N-[2-amino-3-(rho-nitrophenyl)propyl]-trans-cyclohexane-1,2-diamine-N,N',N"-pentaacetic acid (nitro-CHX-A-DTPA).

**[0425]** In another embodiment, the Albumin fusion protein of the invention are attached to an acyclic terpyridine chelator such as 6,6"-bis[[N,N,N",N"- tetra(carboxymethyl)amino]methyl]-4'-(3-amino-4-methoxyphenyl)-2,2':6',2 "- terpyridine (TMT-amine).

**[0426]** In specific embodiments, the macrocyclic chelator which is attached to the the Albumin fusion protein of the invention is 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the the Albumin fusion protein of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo *et al.*, *Clin. Cancer Res. 4*(10):2483-90, 1998; Peterson *et al.*, *Bioconjug. Chem. 10*(4):553-7, 1999; and Zimmerman *et al.*, *Nucl. Med. Biol. 26*(8):943-50, 1999 which are hereby incorporated by reference in their entirety. In addition, U.S. Patents 5,652,361 and 5,756,065, which disclose chelating agents that may be conjugated to antibodies, and methods for making and using them, are hereby incorporated by reference in their entireties. Though U.S. Patents 5,652,361 and 5,756,065 focus on conjugating chelating agents to antibodies, one skilled in the art could readily

adapt the method disclosed therein in order to conjugate chelating agents to other polypeptides.

**[0427]** Bifunctional chelators based on macrocyclic ligands in which conjugation is via an activated arm, or functional group, attached to the carbon backbone of the ligand can be employed as described by M. Moi *et al.*, *J. Amer. Chem. Soc. 49*:2639 (1989) (2-*p*-nitrobenzyl-1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid); S. V. Deshpande *et al.*, *J. Nucl. Med. 31*:473 (1990); G. Ruser *et al.*, *Bioconj. Chem. 1*:345 (1990); C. J. Broan *et al.*, *J. C. S. Chem. Comm. 23*:1739 (1990); and C. J. Anderson *et al.*, *J. Nucl. Med. 36*:850 (1995).

**[0428]** In one embodiment, a macrocyclic chelator, such as polyazamacrocyclic chelators, optionally containing one or more carboxy, amino, hydroxamate, phosphonate, or phosphate groups, are attached to the Albumin fusion protein of the invention. In another embodiment, the chelator is a chelator selected from the group consisting of DOTA, analogues of DOTA, and derivatives of DOTA.

**[0429]** In one embodiment, suitable chelator molecules that may be attached to the the Albumin fusion protein of the invention include DOXA (1-oxa-4,7,10-triazacyclododecanetriacetic acid), NOTA (1,4,7-triazacyclononanetriacetic acid), TETA (1,4,8,11-tetraazacyclotetradecanetetraacetic acid), and THT (4'-(3-amino-4-methoxy-phenyl)-6,6"-bis(N',N'-dicarboxymethyl-*N*-methylhydra zino)-2,2':6',2"-terpyridine), and analogs and derivatives thereof. See, *e.g.*, Ohmono *et al.*, *J. Med. Chem. 35*: 157-162 (1992); Kung *et al.*, *J. Nucl. Med. 25*: 326-332 (1984); Jurisson *et al.*, *Chem. Rev. 93*:1137-1156 (1993); and U.S. Patent No. 5,367,080. Other suitable chelators include chelating agents disclosed in U.S. Patent Nos. 4,647,447; 4,687,659; 4,885,363; EP-A-71564; WO89/00557; and EP-A-232751.

**[0430]** In another embodiment, suitable macrocyclic carboxylic acid chelators which can be used in the present invention include 1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N"*,*N"'*-tetraacetic acid (DOTA); 1,4,8,12-tetraazacyclopentadecane-*N*,*N'*,*N"*,*N"'*-tetraacetic acid (15N4); 1,4,7-triazacyclononane-N,N',N"-triacetic acid (9N3); 1,5,9-triazacyclododecane-N,N',N"-triacetic acid (12N3); and 6-bromoacetamido-benzyl-1,4,8,11-tetraazacyclotetradecane- *N*,*N'*,*N"*,*N"'*-tetraacetic acid (BAT).

**[0431]** A preferred chelator that can be attached to the Albumin Fusion protein of the invention is □-(5-isothiocyanato- 2-methoxyphenyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, which is also known as MeO-DOTA-NCS. A salt or ester of □-(5-isothiocyanato- 2-methoxyphenyl)- 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid may also be used.

**[0432]** Albumin fusion proteins of the invention to which chelators such as those decribed are covalently attached may be labeled (via the coordination site of the chelator) with radionuclides

that are suitable for therapeutic, diagnostic, or both therapeutic and diagnostic purposes. Examples of appropriate metals include Ag, At, Au, Bi, Cu, Ga, Ho, In, Lu, Pb, Pd, Pm, Pr, Rb, Re, Rh, Sc, Sr, Tc, Tl, Y, and Yb. Examples of the radionuclide used for diagnostic purposes are Fe, Gd, $^{111}$In, $^{67}$Ga, or $^{68}$Ga. In another embodiment, the radionuclide used for diagnostic purposes is $^{111}$In, or $^{67}$Ga. Examples of the radionuclide used for therapeutic purposes are $^{166}$Ho, $^{165}$Dy, $^{90}$Y, $^{115m}$In, $^{52}$Fe, or $^{72}$Ga. In one embodiment, the radionuclide used for diagnostic purposes is $^{166}$Ho or $^{90}$Y. Examples of the radionuclides used for both therapeutic and diagnostic purposes include $^{153}$Sm, $^{177}$Lu, $^{159}$Gd, $^{175}$Yb, or $^{47}$Sc. In one embodiment, the radionuclide is $^{153}$Sm, $^{177}$Lu, $^{175}$Yb, or $^{159}$Gd.

**[0433]** Preferred metal radionuclides include $^{90}$Y, $^{99m}$Tc, $^{111}$In, $^{47}$Sc, $^{67}$Ga, $^{51}$Cr, $^{177m}$Sn, $^{67}$Cu, $^{167}$Tm, $^{97}$Ru, $^{188}$Re, $^{177}$Lu, $^{199}$Au, $^{47}$Sc, $^{67}$Ga, $^{51}$Cr, $^{177m}$Sn, $^{67}$Cu, $^{167}$Tm, $^{95}$Ru, $^{188}$Re, $^{177}$Lu, $^{199}$Au, $^{203}$Pb and $^{141}$Ce.

**[0434]** In a particular embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with a metal ion selected from the group consisting of $^{90}$Y, $^{111}$In, $^{177}$Lu, $^{166}$Ho, $^{215}$Bi, and $^{225}$Ac.

**[0435]** Moreover, γ-emitting radionuclides, such as $^{99m}$Tc, $^{111}$In, $^{67}$Ga, and $^{169}$Yb have been approved or under investigation for diagnostic imaging, while β-emitters, such as $^{67}$Cu, $^{111}$Ag, $^{186}$Re, and $^{90}$Y are useful for the applications in tumor therapy. Also other useful radionuclides include γ-emitters, such as $^{99m}$Tc, $^{111}$In, $^{67}$Ga, and $^{169}$Yb, and β-emitters, such as $^{67}$Cu, $^{111}$Ag, $^{186}$Re, $^{188}$Re and $^{90}$Y, as well as other radionuclides of interest such as $^{211}$At, $^{212}$Bi, $^{177}$Lu, $^{86}$Rb , $^{105}$Rh, $^{153}$Sm, $^{198}$Au, $^{149}$Pm, $^{85}$Sr, $^{142}$Pr, $^{214}$Pb, $^{109}$Pd, $^{166}$Ho, $^{208}$Tl, and $^{44}$Sc. Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with the radionuclides described above.

**[0436]** In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with paramagnetic metal ions including ions of transition and lanthanide metal, such as metals having atomic numbers of 21-29, 42, 43, 44, or 57-71, in particular ions of Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu. The paramagnetic metals used in compositions for magnetic resonance imaging include the elements having atomic numbers of 22 to 29, 42, 44 and 58-70.

**[0437]** In another embodiment, Albumin fusion proteins of the invention to which chelators are covalently attached may be labeled with fluorescent metal ions including lanthanides, in particular La, Ce, Pr, Nd, Pm, Sm, Eu (e.g., $^{152}$Eu), Gd, Tb, Dy, Ho, Er, Tm, Yb, and Lu.

**[0438]** In another embodiment, Albumin fusion proteins of the invention to which chelators are

covalently attached may be labeled with heavy metal-containing reporters may include atoms of Mo, Bi, Si, and W.

**[0439]** It is also possible to label the albumin fusion proteins with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

**[0440]** The albumin fusion protein can also be detectably labeled using fluorescence emitting metals such as $^{152}Eu$, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

**[0441]** The albumin fusion proteins can also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged albumin fusion protein is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

**[0442]** Likewise, a bioluminescent compound may be used to label albumin fusion proteins of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

***Transgenic Organisms***

**[0443]** Transgenic organisms that express the albumin fusion proteins of the invention are also included in the invention. Transgenic organisms are genetically modified organisms into which recombinant, exogenous or cloned genetic material has been transferred. Such genetic material is often referred to as a transgene. The nucleic acid sequence of the transgene may include one or more transcriptional regulatory sequences and other nucleic acid sequences such as introns, that may be necessary for optimal expression and secretion of the encoded protein. The transgene may be designed to direct the expression of the encoded protein in a manner that facilitates its recovery from the organism or from a product produced by the organism, *e.g.* from the milk, blood, urine, eggs, hair or seeds of the organism. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species than the species

of the target animal. The transgene may be integrated either at a locus of a genome where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene.

**[0444]** The term "germ cell line transgenic organism" refers to a transgenic organism in which the genetic alteration or genetic information was introduced into a germ line cell, thereby conferring the ability of the transgenic organism to transfer the genetic information to offspring. If such offspring in fact possess some or all of that alteration or genetic information, then they too are transgenic organisms. The alteration or genetic information may be foreign to the species of organism to which the recipient belongs, foreign only to the particular individual recipient, or may be genetic information already possessed by the recipient. In the last case, the altered or introduced gene may be expressed differently than the native gene.

**[0445]** A transgenic organism may be a transgenic animal or a transgenic plant. Transgenic animals can be produced by a variety of different methods including transfection, electroporation, microinjection, gene targeting in embryonic stem cells and recombinant viral and retroviral infection (*see, e.g.*, U.S. Patent No. 4,736,866; U.S. Patent No. 5,602,307; Mullins *et al.* (1993) Hypertension 22(4):630-633; Brenin *et al.* (1997) Surg. Oncol. 6(2)99-110; Tuan (ed.), *Recombinant Gene Expression Protocols*, Methods in Molecular Biology No. 62, Humana Press (1997)). The method of introduction of nucleic acid fragments into recombination competent mammalian cells can be by any method which favors co-transformation of multiple nucleic acid molecules. Detailed procedures for producing transgenic animals are readily available to one skilled in the art, including the disclosures in U.S. Patent No. 5,489,743 and U.S. Patent No. 5,602,307.

**[0446]** A number of recombinant or transgenic mice have been produced, including those which express an activated oncogene sequence (U.S. Patent No. 4,736,866); express simian SV40 T-antigen (U.S. Patent No. 5,728,915); lack the expression of interferon regulatory factor 1 (IRF-1) (U.S. Patent No. 5,731,490); exhibit dopaminergic dysfunction (U.S. Patent No. 5,723,719); express at least one human gene which participates in blood pressure control (U.S. Patent No. 5,731,489); display greater similarity to the conditions existing in naturally occurring Alzheimer's disease (U.S. Patent No. 5,720,936); have a reduced capacity to mediate cellular adhesion (U.S. Patent No. 5,602,307); possess a bovine growth hormone gene (Clutter *et al.* (1996) Genetics 143(4):1753-1760); or, are capable of generating a fully human antibody response (McCarthy (1997) The Lancet 349(9049):405).

**[0447]** While mice and rats remain the animals of choice for most transgenic experimentation, in

some instances it is preferable or even necessary to use alternative animal species. Transgenic procedures have been successfully utilized in a variety of non-murine animals, including sheep, goats, pigs, dogs, cats, monkeys, chimpanzees, hamsters, rabbits, cows and guinea pigs (*see, e.g.*, Kim *et al.* (1997) Mol. Reprod. Dev. 46(4):515-526; Houdebine (1995) Reprod. Nutr. Dev. 35(6):609-617; Petters (1994) Reprod. Fertil. Dev. 6(5):643-645; Schnieke *et al.* (1997) Science 278(5346):2130-2133; and Amoah (1997) J. Animal Science 75(2):578-585).

**[0448]** To direct the secretion of the transgene-encoded protein of the invention into the milk of transgenic mammals, it may be put under the control of a promoter that is preferentially activated in mammary epithelial cells. Promoters that control the genes encoding milk proteins are preferred, for example the promoter for casein, beta lactoglobulin, whey acid protein, or lactalbumin (see, *e.g.*, DiTullio (1992) BioTechnology 10:74-77; Clark *et al.* (1989) BioTechnology 7:487-492; Gorton *et al.* (1987) BioTechnology 5:1183-1187; and Soulier *et al.* (1992) FEBS Letts. 297:13). The transgenic mammals of choice would produce large volumes of milk and have long lactating periods, for example goats, cows, camels or sheep.

**[0449]** An albumin fusion protein of the invention can also be expressed in a transgenic plant, *e.g.* a plant in which the DNA transgene is inserted into the nuclear or plastidic genome. Plant transformation procedures used to introduce foreign nucleic acids into plant cells or protoplasts are known in the art. See, in general, Methods in Enzymology Vol. 153 ("Recombinant DNA Part D") 1987, Wu and Grossman Eds., Academic Press and European Patent Application EP 693554. Methods for generation of genetically engineered plants are further described in US Patent No. 5,283,184, US Patent No. 5, 482,852, and European Patent Application EP 693 554, all of which are hereby incorporated by reference.

***Pharmaceutical or Therapeutic Compositions***

**[0450]** The albumin fusion proteins of the invention or formulations thereof may be administered by any conventional method including parenteral (*e.g.* subcutaneous or intramuscular) injection or intravenous infusion. The treatment may consist of a single dose or a plurality of doses over a period of time.

**[0451]** While it is possible for an albumin fusion protein of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation, together with one or more acceptable carriers. The carrier(s) must be "acceptable" in the sense of being compatible with the albumin fusion protein and not deleterious to the recipients thereof. Typically, the carriers will be water or saline which will be sterile and pyrogen free. Albumin fusion proteins of the invention are particularly well suited to formulation in aqueous carriers such as sterile pyrogen

free water, saline or other isotonic solutions because of their extended shelf-life in solution. For instance, pharmaceutical compositions of the invention may be formulated well in advance in aqueous form, for instance, weeks or months or longer time periods before being dispensed.

**[0452]** For example, formulations containing the albumin fusion protein may be prepared taking into account the extended shelf-life of the albumin fusion protein in aqueous formulations. As discussed above, the shelf-life of many of these Therapeutic proteins are markedly increased or prolonged after fusion to HA.

**[0453]** In instances where aerosol administration is appropriate, the albumin fusion proteins of the invention can be formulated as aerosols using standard procedures. The term "aerosol" includes any gas-borne suspended phase of an albumin fusion protein of the instant invention which is capable of being inhaled into the bronchioles or nasal passages. Specifically, aerosol includes a gas-borne suspension of droplets of an albumin fusion protein of the instant invention, as may be produced in a metered dose inhaler or nebulizer, or in a mist sprayer. Aerosol also includes a dry powder composition of a compound of the instant invention suspended in air or other carrier gas, which may be delivered by insufflation from an inhaler device, for example. See Ganderton & Jones, *Drug Delivery to the Respiratory Tract, Ellis Horwood* (19 87); Gonda (1990) *Critical Reviews in Therapeutic Drug Carrier Systems* 6:273-313; and Raeburn *et al,.* (1992) *Pharmacol. Toxicol. Methods* 27:143-159.

**[0454]** The formulations of the invention are also typically non-immunogenic, in part, because of the use of the components of the albumin fusion protein being derived from the proper species. For instance, for human use, both the Therapeutic protein and albumin portions of the albumin fusion protein will typically be human. In some cases, wherein either component is non human-derived, that component may be humanized by substitution of key amino acids so that specific epitopes appear to the human immune system to be human in nature rather than foreign.

**[0455]** The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the albumin fusion protein with the carrier that constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

**[0456]** Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation appropriate for the intended recipient; and aqueous and

non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules, vials or syringes, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders. Dosage formulations may contain the Therapeutic protein portion at a lower molar concentration or lower dosage compared to the non-fused standard formulation for the Therapeutic protein given the extended serum half-life exhibited by many of the albumin fusion proteins of the invention.

**[0457]** As an example, when an albumin fusion protein of the invention comprises one of the proteins listed in the "Therapeutic Protein:X" column of Table 1 as one or more of the Therapeutic protein regions, the dosage form can be calculated on the basis of the potency of the albumin fusion protein relative to the potency of the therapeutic protein alone, while taking into account the prolonged serum half-life and shelf-life of the albumin fusion proteins compared to that of native therapeutic protein. For example, if the therapeutic protein is typically administered at 0.3 to 30.0 IU/kg/week, or 0.9 to 12.0 IU/kg/week, given in three or seven divided doses for a year or more. In an albumin fusion protein consisting of full length HA fused to a therpeutic protein, an equivalent dose in terms of units would represent a greater weight of agent but the dosage frequency can be reduced, for example to twice a week, once a week or less.

**[0458]** Formulations or compositions of the invention may be packaged together with, or included in a kit with, instructions or a package insert referring to the extended shelf-life of the albumin fusion protein component. For instance, such instructions or package inserts may address recommended storage conditions, such as time, temperature and light, taking into account the extended or prolonged shelf-life of the albumin fusion proteins of the invention. Such instructions or package inserts may also address the particular advantages of the albumin fusion proteins of the inventions, such as the ease of storage for formulations that may require use in the field, outside of controlled hospital, clinic or office conditions. As described above, formulations of the invention may be in aqueous form and may be stored under less than ideal circumstances without significant loss of therapeutic activity.

**[0459]** Albumin fusion proteins of the invention can also be included in nutraceuticals. For instance, certain albumin fusion proteins of the invention may be administered in natural products, including milk or milk product obtained from a transgenic mammal which expresses albumin fusion protein. Such compositions can also include plant or plant products obtained

from a transgenic plant which expresses the albumin fusion protein. The albumin fusion protein can also be provided in powder or tablet form, with or without other known additives, carriers, fillers and diluents. Nutraceuticals are described in Scott Hegenhart, *Food Product Design*, Dec. 1993.

**[0460]** The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of an albumin fusion protein of the invention or a polynucleotide encoding an albumin fusion protein of the invention ("albumin fusion polynucleotide") in a pharmaceutically acceptable carrier.

**[0461]** The albumin fusion protein and/or polynucleotide will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the albumin fusion protein and/or polynucleotide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

**[0462]** As a general proposition, the total pharmaceutically effective amount of the albumin fusion protein administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the albumin fusion protein is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

**[0463]** As noted above, the albumin fusion protein of the invention has a higher plasma stablity compared to the Therapeutic protein portion (or fragment or variant thereof) alone. This increase in plasma stability should be taken into account when determining the effective amount of the albumin fusion protein to be administered per dose and the dosing administration schedule. In particular, higher plasma stability may allow the albumin fusion protein to be administered at a lower dose at the same frequency of administrations, or alternatively, may allow the albumin fusion protein to be administered in fewer dosings. Preferably, the higher stability allows the albumin fusion protein of the invention to be administered less often in fewer dosings. More

preferably, the albumin fusion protein can be administered once every two weeks. Still more preferably, the albumin fusion protein can be administered once every three, four, five, or more weeks depending on the pharmacokinetics of the albumin fusion protein. For example, as discussed above, the pharmacokinetics of an IFN-alpha-HSA fusion protein supports a dosing regimen of once every 2-4 weeks or more, and even dosing at intervals of 4 weeks or more than every 4 weeks.

**[0464]** The effective amount of the albumin fusion protein to be administered per dose can also be denoted as the total formulated albumin fusion protein concentration given per dose. In one embodiment, the total formulated albumin fusion protein concentration administered to a patient per dose is in the range of about 10 ug/dose to about 2000 ug/dose. More preferably, the total concentration is in the range of about 100 ug/dose to about 1000 ug/dose, or alternatively, about 1000 ug/dose to about 1200 ug/dose or about 900 ug/dose to about 1800 ug/dose.

**[0465]** In a specific embodiment, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is dosed in a total formulated concentration of about 90 ug/dose to about 2000 ug/dose. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is dosed in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose, about 900 ug/dose to about 1200 ug/dose, about 900 ug/dose to about 1800 ug/dose and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose. In additional preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is dosed in a total formulated concentration of 600 ug/dose, 720 ug/dose, 800 ug/dose, 900 ug/dose, 1000 ug/dose, 1200 ug/dose, 1500 ug/dose, 1800 ug/dose, or 2000 ug/dose. In additional embodiments, the total formulated dose of an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered either alone or in combination with an antiviral compound, such as ribavirin. In additionally preferred embodiments, the total formulated dose of an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered in combination with one, two, three, or more antiviral compounds, including, but not limited to, ribavirin and optionally another antiviral compound.

**[0466]** In an additional embodiment, the total formulated concentration of an IFN-alpha-HSA fusion proteins of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to treat a patient infected with HCV. In a specific embodiment, the IFN-alpha-HSA fusion proteins of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) are administered to a Treatment naïve patient with HCV either alone or in combination with an effective amount of an antiviral compound, such as ribavirin, in a total formulated concentration of about 90 ug/dose to about 2000 ug/dose. In more preferred embodiments, the IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve patient with HCV either alone or in combination with an effective amount of antiviral compound, such as ribavirin, in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose, about 900 ug/dose to about 1200 ug/dose, about 900 ug/dose to about 1800 ug/dose and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose. In additional preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve patient with HCV either alone or in combination with an effective amount of antiviral compound, such as ribavirin, in a total formulated concentration of 600 ug/dose, 720 ug/dose, 800 ug/dose, 900 ug/dose, 1000 ug/dose, 1200 ug/dose, 1500 ug/dose, 1800 ug/dose, or 2000 ug/dose.

**[0467]** In an additional embodiment, the total formulated concentration of an IFN-alpha-HSA fusion proteins of the invention are administered to a Treatment naïve patient with HCV in combination with an effective amount of one or more antiviral compounds, including, for example, ribavirin, in a total formulated concentration of about 90 ug/dose to about 2000 ug/dose. In additional preferred embodiments, the IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve patient with HCV in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound, in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose, about 900 ug/dose to about 1200 ug/dose, about 900 ug/dose to about 1800 ug/dose and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose. In additional preferred embodiments, an IFN-alpha-HSA fusion

protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve patient with HCV in combination with an effective amount of one, two, three, or more antiviral compounds, including, for example, ribavirin, in a total formulated concentration of 600 ug/dose, 720 ug/dose, 800 ug/dose, 900 ug/dose, 1000 ug/dose, 1200 ug/dose, 1500 ug/dose, 1800 ug/dose, or 2000 ug/dose.

**[0468]** In an additional embodiment, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced patient with HCV either alone or in combination with an effective amount of antiviral compound, such as ribavirin, in a total formulated concentration of about 90 ug/dose to about 2000 ug/dose. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced patient with HCV either alone or in combination with an effective amount of antiviral compound, such as ribavirin, in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose, about 900 ug/dose to about 1200 ug/dose, about 900 ug/dose to about 1800 ug/dose and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose. In additional preferred embodiments, an IFN-alpha-HSA fusion proteins of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced patient with HCV either alone or in combination with an effective amount of antiviral compound, such as ribavirin, in a total formulated concentration of 600 ug/dose, 720 ug/dose, 800 ug/dose, 900 ug/dose, 1000 ug/dose, 1200 ug/dose, 1500 ug/dose, 1800 ug/dose, or 2000 ug/dose.

**[0469]** In an additional embodiment, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced patient with HCV in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound, in a total formulated concentration of about 90 ug/dose to about 2000 ug/dose. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced patient with HCV in combination with one, two, three, or more antiviral compounds,

including, for example, ribavirin and optionally another antiviral compound, in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose, about 900 ug/dose to about 1200 ug/dose, about 900 ug/dose to about 1800 ug/dose and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose. In additional preferred embodiments, an IFN-alpha-HSA fusion proteins of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced patient with HCV in combination with an effective amount of one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound, in a total formulated concentration of 600 ug/dose, 720 ug/dose, 800 ug/dose, 900 ug/dose, 1000 ug/dose, 1200 ug/dose, 1500 ug/dose, 1800 ug/dose, or 2000 ug/dose.

**[0470]** The total formulated concentration of the albumin fusion protein and the dosing interval in which the dosing interval at which the albumin fusion protein will administered will vary depending on the desired effect and the particular therapeutic protein adminstered. In one embodiment, the total formulated albumin fusion protein concentration administered to a patient per dose is in the range of about 10 ug/dose to about 2000 ug/dose once a week, once every two weeks, once every three weeks, once every four weeks or more. More preferably, the total concentration is in the range of about 100 ug/dose to about 1000 ug/dose once a week, once every two weeks, once every three weeks, once every four weeks or more, or alternatively, about 1000 ug/dose to about 1200 ug/dose or about 900 ug/dose to about 1800 ug/dose once a week, once every two weeks, once every three weeks, once every four weeks or more.

**[0471]** In a specific embodiment, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered at a total formulated concentration of about 90 ug/dose to about 2000 ug/dose once every two, three, four, or five weeks. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is dosed in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1200 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1800 ug/dose once every one, two, three, four or five weeks; and most preferably in a total formulated concentration of about 1200 ug/dose to 1800 ug/dose once every one, two, three, four or five weeks. In additional embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249,

2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered at a total formulated concentration of about 600 ug/dose once every one, two, three, four or five weeks; 800 ug/dose once every one, two, three, four or five weeks, 900 ug/dose once every one, two, three, four or five weeks; 1000 ug/dose once every one, two, three, four or five weeks; 1200 ug/dose once every one, two, three, four or five weeks; 1500 ug/dose once every one, two, three, four or five weeks; 1600 ug/dose once every one, two, three, four or five weeks; 1800 ug/dose once every one, two, three, four or five weeks; or 2000 ug/dose once every one, two, three, four or five weeks. In more preferred embodiments, the IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered at a total formulated concentration of 900 ug/dose once every two weeks, and more preferably at a total concentration of 1200 ug/dose once every two weeks, 1200 ug/dose once every four weeks, or 1800 ug/dose once every four weeks. In additional embodiments, the total formulated dose of an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered either alone or in combination with an antiviral compound, such as ribavirin. In additional preferred embodiments, the total formulated dose of an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound.

**[0472]** In specific embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient at a total formulated concentration of about 90 ug/dose to about 2000 ug/dose once every two, three, four, or five weeks either alone or in combination with an antiviral compound, such as ribavirin. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1200 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1800 ug/dose once every one, two, three, four or five weeks; and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose once

every one, two, three, four or five weeks either alone or in combination with an antiviral compound, including, such as ribavirin. In additional embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient at a total formulated concentration of about 600 ug/dose once every one, two, three, four or five weeks; 800 ug/dose once every one, two, three, four or five weeks, 900 ug/dose once every one, two, three, four or five weeks; 1000 ug/dose once every one, two, three, four or five weeks; 1200 ug/dose once every one, two, three, four or five weeks; 1500 ug/dose once every one, two, three, four or five weeks; 1600 ug/dose once every one, two, three, four or five weeks; 1800 ug/dose once every one, two, three, four or five weeks; or 2000 ug/dose once every one, two, three, four or five weeks either alone or in combination with an antiviral compound, such as ribavirin.

**[0473]** In preferred specific embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient at a total formulated concentration of about 90 ug/dose to about 2000 ug/dose once every two, three, four, or five weeks in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound.. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1200 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1800 ug/dose once every one, two, three, four or five weeks; and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose once every one, two, three, four or five weeks in combination with one or more antiviral compounds, including, for example, ribavirin in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound. In additional embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient at a total formulated concentration of about 600 ug/dose once every one, two, three, four or five weeks; 800 ug/dose once every one, two, three, four or five weeks, 900 ug/dose once every one, two, three, four or

five weeks; 1000 ug/dose once every one, two, three, four or five weeks; 1200 ug/dose once every one, two, three, four or five weeks; 1500 ug/dose once every one, two, three, four or five weeks; 1600 ug/dose once every one, two, three, four or five weeks; 1800 ug/dose once every one, two, three, four or five weeks; or 2000 ug/dose once every one, two, three, four or five weeks in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound.

**[0474]** In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient at a total formulated concentration of 900 ug/dose once every two weeks, and more preferably at a total concentration of 1200 ug/dose once every two weeks, 1200 ug/dose once every four weeks, or 1800 ug/dose once every four weeks, either alone or in combination with an antiviral compound, such as ribavirin. In most preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment naïve HCV patient at a total formulated concentration of 900 ug/dose once every two weeks, and more preferably at a total concentration of 1200 ug/dose once every two weeks, 1200 ug/dose once every four weeks, or 1800 ug/dose once every four weeks, in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound.

**[0475]** In additional specific embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient at a total formulated concentration of about 90 ug/dose to about 2000 ug/dose once every two, three, four, or five weeks either alone or in combination with an antiviral compound, such as ribavirin. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1200 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1800 ug/dose once every one, two, three, four or five weeks; and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose once every one, three, four or five weeks, or most preferably every two

weeks either alone or in combination with an antiviral compound, such as ribavirin. In additional embodiments, an IFN-alpha-HSA fusion proteins of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient at a total formulated concentration of about 600 ug/dose once every one, two, three, four or five weeks; 800 ug/dose once every one, two, three, four or five weeks, 900 ug/dose once every one, two, three, four or five weeks; 1000 ug/dose once every one, two, three, four or five weeks; 1200 ug/dose once every one, two, three, four or five weeks; 1500 ug/dose once every one, two, three, four or five weeks; 1600 ug/dose once every one, two, three, four or five weeks; 1800 ug/dose once every one, two, three, four or five weeks; or 2000 ug/dose once every one, two, three, four or five weeks either alone or in combination with an antiviral compound, such as ribavirin.

**[0476]** In more specific embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient at a total formulated concentration of about 90 ug/dose to about 2000 ug/dose once every two, three, four, or five weeks in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound. In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient in a total formulated concentration of about 900 ug/dose to about 2000 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1200 ug/dose once every one, two, three, four or five weeks; about 900 ug/dose to about 1800 ug/dose once every one, two, three, four or five weeks; and most preferably in a total formulated concentration of about 1200 ug/dose to about 1800 ug/dose once every one, three, four or five weeks, or most preferably every two weeks in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound. In additional embodiments, an IFN-alpha-HSA fusion proteins of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient at a total formulated concentration of about 600 ug/dose once every one, two, three, four or five weeks; 800 ug/dose once every one, two, three, four or five weeks, 900 ug/dose once every one, two, three, four or five weeks; 1000 ug/dose once every one, two, three, four or five weeks; 1200 ug/dose once every one, two, three, four or five weeks; 1500 ug/dose once every

one, two, three, four or five weeks; 1600 ug/dose once every one, two, three, four or five weeks; 1800 ug/dose once every one, two, three, four or five weeks; or 2000 ug/dose once every one, two, three, four or five weeks in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound.

**[0477]** In more preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient at a total formulated concentration of 900 ug/dose once every two weeks, and more preferably at a total concentration of 1200 ug/dose once every two weeks, 1200 ug/dose once every four weeks, or 1800 ug/dose once every four weeks, either alone or in combination with an antiviral compound, such as ribavirin. In most preferred embodiments, an IFN-alpha-HSA fusion protein of the invention (e.g., produced by CIDs 2249, 2343, 2366, 2381, 2382, 2410, 3165, 3422, 3423, 3424, 3476, 3960, 4290, 4291, 4292, 4295, or 4296) is administered to a Treatment experienced HCV patient at a total formulated concentration of 900 ug/dose once every two weeks, and more preferably at a total concentration of 1200 ug/dose once every two weeks, 1200 ug/dose once every four weeks, or 1800 ug/dose once every four weeks, in combination with one, two, three, or more antiviral compounds, including, for example, ribavirin and optionally another antiviral compound.

**[0478]** Albumin fusion proteins and/or polynucleotides can be are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

**[0479]** Albumin fusion proteins and/or polynucleotides of the invention are also suitably administered by sustained-release systems. Examples of sustained-release albumin fusion proteins and/or polynucleotides are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection

and infusion. Additional examples of sustained-release albumin fusion proteins and/or polynucleotides include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

**[0480]** Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

**[0481]** Sustained-release albumin fusion proteins and/or polynucleotides also include liposomally entrapped albumin fusion proteins and/or polynucleotides of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the albumin fusion protein and/or polynucleotide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

**[0482]** In yet an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

**[0483]** Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

**[0484]** For parenteral administration, in one embodiment, the albumin fusion protein and/or polynucleotide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the

Therapeutic.

**[0485]** Generally, the formulations are prepared by contacting the albumin fusion protein and/or polynucleotide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

**[0486]** The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates (including, for example, Tween-20), poloxamers, or PEG.

**[0487]** The albumin fusion protein is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

**[0488]** Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Albumin fusion proteins and/or polynucleotides generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

**[0489]** Albumin fusion proteins and/or polynucleotides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous albumin fusion protein and/or polynucleotide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by

reconstituting the lyophilized albumin fusion protein and/or polynucleotide using bacteriostatic Water-for-Injection.

**[0490]** In a specific and preferred embodiment, the Albumin fusion protein formulations comprises 0.01 M sodium phosphate, 0.15 mM sodium chloride, 0.16 micromole sodium octanoate/milligram of fusion protein, 15 micrograms/milliliter polysorbate 80, pH 7.2. In another specific and preferred embodiment, the Albumin fusion protein formulations consists 0.01 M sodium phosphate, 0.15 mM sodium chloride, 0.16 micromole sodium octanoate/milligram of fusion protein, 15 micrograms/milliliter polysorbate 80, pH 7.2. The pH and buffer are chosen to match physiological conditions and the salt is added as a tonicifier. Sodium octanoate has been chosen due to its reported ability to increase the thermal stability of the protein in solution. Finally, polysorbate has been added as a generic surfactant, which lowers the surface tension of the solution and lowers non-specific adsorption of the albumin fusion protein to the container closure system.

**[0491]** The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the albumin fusion proteins and/or polynucleotides of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the albumin fusion proteins and/or polynucleotides may be employed in conjunction with other therapeutic compounds.

**[0492]** The albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum.* In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with alum. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, vaccines directed toward protection against MMR

(measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, *Haemophilus influenzae* B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

**[0493]** The albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with other therapeutic agents. Albumin fusion protein and/or polynucleotide agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

**[0494]** In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROME™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are

administered in combination with heparin and aspirin.

**[0495]** In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, compositions of the invention are administered in combination with tissue plasminogen activator and aspirin.

**[0496]** In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINE™), and ticlopidine (e.g., TICLID™).

**[0497]** In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with albumin fusion proteins and/or polynucleotides of the invention is contemplated for the prevention, diagnosis, and/or treatment of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with albumin fusion proteins and/or polynucleotides of the invention is contemplated for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

**[0498]** In certain embodiments, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to,

RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with albumin fusion proteins and/or polynucleotides of the invention to treat AIDS and/or to prevent or treat HIV infection.

**[0499]** Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

**[0500]** Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

**[0501]** Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

**[0502]** Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

**[0503]** Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine recpetor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

**[0504]** Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

**[0505]** Additional antiretroviral agents include hydroxyurea-like compunds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors sucha as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

**[0506]** Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV

entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

**[0507]** Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-alpha2a, IFN-alpha2b, or IFN-beta; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al., PNAS 94*:11567-72 (1997); Chen *et al., Nat. Med. 3*:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

**[0508]** In a further embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with one or more antiviral agent. Antiviral agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, acyclovir, ribavirin, ribavirin analog, amantadine, remantidine, maxamine, or thymalfasin. Specifically, interferon albumin fusion protein can be administered in combination with any of these agents. Moreover, interferon alpha albumin fusion protein can also be admistered with any of these agents, and preferably, interferon alpha 2a or 2b albumin fusion protein can be administered with any of these agents. Furthermore, interferon beta albumin fusion protein can also be admistered with any of these agents. Additionally, any of the IFN hybrids albumin fusion proteins can be administered in combination with any of these

agents.

**[0509]** In a most preferred embodiment, an interferon albumin fusion protein of the invention is administered in combination with ribavirin or a ribavirin analog. In a preferred embodiment, the ribavirin or ribavirin analogs that may be administered in combination with an interferon albumin fusion protein include but are not limited to COPEGUS® (Hoffman-La Roche, Nutley, N.J.), REBETOL® (Schering Corp., Kenilworth, N.J.), VIRAZOLE® (Valeant, Costa Mesa, CA), RIBAVIN™ (Lupin, Baltimore, MD), RIBAZID™ (Epla, Kirachi, Pakistan), tribavirin, VIRAMIDINE™ (Valeant, Costa Mesa, CA), and RIBASPHERE™ (Three Rivers Pharmaceuticals, Cranberry Township, PA). In a further preferred embodiment, interferon alpha albumin fusion protein is administered in combination with ribavirin or ribavirin analog. In a further preferred embodiment, interferon alpha 2a albumin fusion protein is administered in combination with ribavirin or ribavirin analog. In a further preferred embodiment, interferon alpha 2b albumin fusion protein is administered in combination with ribavirin or ribavirin analog. In a further preferred embodiment, interferon beta albumin fusion protein is administered in combination with ribavirin or ribavirin analog. In a further preferred embodiment, hybrid interferon albumin fusion protein is administered in combination with ribavirin or ribavirin analog.

**[0510]** In a further embodiment, the albumin fusion proteins and/or polynucleotides of the invention may be administered alone or in combination with one or more antiviral agents for the treatment of viral infection. In a preferred embodiment, an interferon-albumin fusion protein of the invention may be administered in combination with one or more antiviral agents. In an additional preferred embodiment, the viral infection results from infection with a hepatitis virus. In a most preferred embodiment, the hepatitis virus is hepatitis C virus (HCV). Antiviral agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, small-molecule inhibitors of viral enzymes, small-molecule inhibitors of RNA polymerase, nucleic acid based antiviral agents, antisense oligonucleotide inhibitors, thiazolides, novel immunomodulatory agents, and interferon enhancers. Anti-viral enzyme inhibitors that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, VX-950 (protease inhibitor, Vertex, Cambridge, MA), VX-497 (merimepodib, oral IMPDH inhibitor, Vertex, Cambridge, MA), BILB 1941 (protease inhibitor, Boehringer Ingelheim, Germany), SCH7 (protease inhibitor, Schering Corp., Kenilworth, N.J.), MX-3253 (glucosidase inhibitor, Migenix, Vancouver, BC), IDN-6556 (caspase inhibitor, Pfizer, New York, NY),

UT231B (glucosidase inhibitor, United Therapeutics, Silver Spring, MD), R1626 (viral protease inhibitor, F. Hoffman-La Roche, Switzerland), ITMN-B (ITMN-191, protease inhibitor, InterMune, Brisbane, CA), Celgosivir (MBI-3253, α-glucosidase inhibitor, Migenix, Inc., Vancouver, B.C.), SCH 503034 (protease inhibitor, Schering Corp., Kenilworth, N.J.), ACH 806 (GS9132, oral protease inhibitor, Achillion, New Haven, CT / Gilead Sciences, Foster City, CA). Anti-viral polymerase inhibitors that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention may be nucleoside analogs or non-nucleoside inhibitors (NNIs). In a preferred embodiment, the anti-viral polymerase inhibitors inhibit HCV RNA polymerase. In one embodiment, the anti-viral polymerase inhibitors may be nucleoside analogs including, but not limited to, NM283 (oral prodrug of 23'-C-methyl-cytidine, Idenix, Cambride, MA), and 2'-C-methyl nucleosides. In another emboidment, the anti-viral polymerase inhibitors may be non-nucleoside inhibitors, including, but not limited to, JTK-103, JTK-003, and JTK-109 (Japan Tabacco, Tokyo, Japan), R803 (Rigel, South San Francisco, CA), HCV-371, HCV-086, and HCV-796 (ViroPharm, Exton, PA / Wyeth, Madison, NJ), and XTL-2125 (BC2125, XTLbio, New York, NY). Anti-viral nucleic acid based agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, antisense oligonucleotides, ribozymes, and siRNAs or short hairpin RNAs (shRNA). Anti-viral antisense oligonucleotide inhibitor agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, NEUGENE® AVI-4065 (AVI Biopharma, Portland, OR). In another embodiment, a thiazolide may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention. In a preferred embodiment, thiazolides that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to ALINIA® (nitazoxanide, Romark Laboratories, L.C., Tampa, FL). Anti-viral immunomodulatory agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, ZADXIN® (thymosin alpha 1, thymalfasin, SciClone Pharmaceuticals Int'l, Hong Kong) and toll-like receptor (TLR) agonists, including, but not limited to, ANA245 (TLR-7 agonist, Anadys Pharmaceuticals, San Diego, CA), ANA975 (oral prodrug of ANA245, Anadys Pharmaceuticals, San Diego, CA), and CPG-10101 (ACTILON™, TLR-9 agonist, Coley Pharmaceutical Group, Wellesley, MA). Interferon enhancers that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to EMZ702 (Transition Therapeutics, Toronto, Ontario). Moreover, anti-viral

antibodies that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to Tarvacin (humanized monoclonal antibody that targets phosphatidylserine on the surface of tumor endothelial cells, Peregrine Pharmaceuticals, Inc., Tustin, CA).

**[0511]** In a preferred embodiment the albumin fusion protein that may be administered alone or in combination with one or more of the antiviral agents encompassed by the invention is an inteferon-albumin fusion protein. In additional embodiment, the interferon portion of the interferon-albumin fusion protein is an interferon alpha. Non-limiting examples of interferon alpha encompassed by the invention include, but are not limited to, the interferon alpha proteins disclosed in the Therapeutic protein column of Table 1. In particular embodiments, the interferon alpha portion consists or alternatively comprises interferon alpha-2a, interferon alpha-2b, interferon alpha-2c, consensus interferon, interferon alfacon-1, interferon alpha-n1, interferon alpha-n3, any commercially available form of interferon alpha, such as, for example, INTRON® A (Schering Corp., Kenilworth, N.J.), ROFERON® A (Hoffman-La Roche, Nutley, N.J.), Berofor alpha inteferon (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefied, Conn.), OMNIFERON™ (Viragen, Inc., Plantation, FL), MULTIFERON™ (Viragen, Inc., Plantation, FL) WELLFERON® (GlaxoSmithKline, London, Great Britian), INFERGEN® (Amgen, Inc., Thousands Oaks, CA), SUMIFERON® (Sumitomo, Japan), BELEROFON® (Nautilus Biotech, France), MAXY-ALPHA™ (Maxygen, Redwood City, CA / Hoffman-La Roche, Nutley, N.J.), or any purified interferon alpha product or a fragment thereof. In further embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein consists or alternatively comprises interferon alpha modified or formulated for extended or controlled release. For example, the interferon alpha portion consists, or alternatively comprises commercially available extended release or controlled release interferon alpha, including, but not limited to interferon-alpha-XL (Flamel Technologies, France) and LOCTERON™ (BioLex Therapeutics/OctoPlus, Pittsboro, NC). In additional embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein may be modified by the attachment of chemical moieties. For example, the inteferon alpha portion may be modified by pegylation. Accordingly, in additional embodiments, the interferon alpha portion of the IFN-alpha-HSA fusion protein consists or alternatively comprises pegylated forms of interferon alpha-2a, 2b, or consensus interferon and include, but are not limited to, a commercially available pegylated interferon alpha, such as, for example, PEG-INTRON® (Schering Corp., Kenilworth, N.J.), PEGASYS® (Hoffman-La Roche, Nutley, N.J.), PEG-OMNIFERON™ (Viragen, Inc., Plantation, FL) or a fragment thereof.In an additional

preferred embodiment the interferon portion of the albumin fusion protein is interferon alpha 2a or 2b interferon, interferon albumin fusion protein can be administered in combination with any of these agents. Moreover, in another embodiment, the interferon portion of the interferon-albumin fusion protein is an interferon beta or an interferon hybrids. In a further embodiment, the unfused interferon portion of the inteferon-albumin fusion protein may be used alone or in combination with one or more of the antiviral agents encompassed by the invention.

**[0512]** In other embodiments, albumin fusion proteins and/or polynucleotides of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with

ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

**[0513]** In a further embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

**[0514]** In other embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

**[0515]** In other embodiments, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active

metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

**[0516]** In an additional embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

**[0517]** In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered alone or as part of a combination therapy, either in vivo to patients or in vitro to cells, for the treament of cancer. In a specific embodiment, the albumin fusion proteins, particularly IL-2-albumin fusions, are administered repeatedly during passive immunotherapy for cancer, such as adoptive cell transfer therapy for metastatic melanoma as described in Dudley *et al.* (Science Express, 19 September 2002., at www.scienceexpress.org, hereby incorporated by reference in its entirety).

**[0518]** In certain embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-

amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

**[0519]** In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

**[0520]** Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

**[0521]** Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

**[0522]** Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

**[0523]** A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4;

protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

**[0524]** Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

**[0525]** Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not limited

to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not limited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

**[0526]** In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

**[0527]** In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

**[0528]** In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

**[0529]** In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

**[0530]** In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

**[0531]** In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

**[0532]** In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are $^{90}Y$ and $^{111}In$.

**[0533]** In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with cytokines. Cytokines that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, albumin fusion proteins and/or polynucleotides of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

**[0534]** In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha

(LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

**[0535]** In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

**[0536]** In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the albumin fusion proteins and/or polynucleotides of the

invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

**[0537]** In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

**[0538]** In certain embodiments, albumin fusion proteins and/or polynucleotides of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

**[0539]** In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

**[0540]** In another embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit $Na^+$-$K^+$-$2Cl^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

**[0541]** In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with treatments for endocrine and/or hormone imbalance

disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, $^{127}I$, radioactive isotopes of iodine such as $^{131}I$ and $^{123}I$; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-$T_4$™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-$T_3$™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; $Ca^{2+}$ channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

**[0542]** Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™,

BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

**[0543]** Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™

(dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone); bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), ciglitazone, pioglitazone, and alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide).

**[0544]** In one embodiment, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

**[0545]** In an additional embodiment, the albumin fusion proteins and/or polynucleotides of the

invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin $B_{12}$, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™), hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

**[0546]** In certain embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

**[0547]** In other embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benztropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

**[0548]** In another embodiment, albumin fusion proteins and/or polynucleotides of the invention are administered in combination with vasodilating agents and/or calcium channel blocking

agents. Vasodilating agents that may be administered with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the albumin fusion proteins and/or polynucleotides of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

**[0549]** In certain embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the albumin fusion protein and/or polynucleotide of the invention include, but are not limited to, $H_2$ histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of $H^+$, $K^+$ ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, trifluprornazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

**[0550]** In additional embodiments, the albumin fusion proteins and/or polynucleotides of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

**[0551]** The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions

comprising albumin fusion proteins of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

***Gene Therapy***

**[0552]** Constructs encoding albumin fusion proteins of the invention can be used as a part of a gene therapy protocol to deliver therapeutically effective doses of the albumin fusion protein. A preferred approach for *in vivo* introduction of nucleic acid into a cell is by use of a viral vector containing nucleic acid, encoding an albumin fusion protein of the invention. Infection of cells with a viral vector has the advantage that a large proportion of the targeted cells can receive the nucleic acid. Additionally, molecules encoded within the viral vector, *e.g.*, by a cDNA contained in the viral vector, are expressed efficiently in cells which have taken up viral vector nucleic acid.

**[0553]** Retrovirus vectors and adeno-associated virus vectors can be used as a recombinant gene delivery system for the transfer of exogenous nucleic acid molecules encoding albumin fusion proteins *in vivo*. These vectors provide efficient delivery of nucleic acids into cells, and the transferred nucleic acids are stably integrated into the chromosomal DNA of the host. The development of specialized cell lines (termed "packaging cells") which produce only replication-defective retroviruses has increased the utility of retroviruses for gene therapy, and defective retroviruses are characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A.D. (1990) *Blood* 76:27 1). A replication defective retrovirus can be packaged into virions which can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F.M. *et al.*, (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals.

**[0554]** Another viral gene delivery system useful in the present invention uses adenovirus-derived vectors. The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner *et al.*, *BioTechniques* 6:616 (1988); Rosenfeld *et al.*, Science 252:431-434 (1991); and Rosenfeld *et al.*, *Cell* 68:143-155 (1992). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (*e.g.*, Ad2, Ad3, Ad7 etc.) are known to those skilled in the art. Recombinant adenoviruses can be advantageous in certain circumstances in that they are not

capable of infecting nondividing cells and can be used to infect a wide variety of cell types, including epithelial cells (Rosenfeld *et al.*, (1992) cited supra). Furthermore, the virus particle is relatively stable and amenable to purification and concentration, and as above, can be modified so as to affect the spectrum of infectivity. Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (*e.g.*, retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner *et al.*, cited supra; Haj-Ahmand *et al.*, J. Virol. 57:267 (1986)).

**[0555]** In another embodiment, non-viral gene delivery systems of the present invention rely on endocytic pathways for the uptake of the subject nucleotide molecule by the targeted cell. Exemplary gene delivery systems of this type include liposomal derived systems, poly-lysine conjugates, and artificial viral envelopes. In a representative embodiment, a nucleic acid molecule encoding an albumin fusion protein of the invention can be entrapped in liposomes bearing positive charges on their surface (*e.g.*, lipofectins) and (optionally) which are tagged with antibodies against cell surface antigens of the target tissue (Mizuno *et al.* (1992) *No Shinkei Geka* 20:547-5 5 1; PCT publication W091/06309; Japanese patent application 1047381; and European patent publication EP-A-43075).

**[0556]** Gene delivery systems for a gene encoding an albumin fusion protein of the invention can be introduced into a patient by any of a number of methods. For instance, a pharmaceutical preparation of the gene delivery system can be introduced systemically, *e.g.* by intravenous injection, and specific transduction of the protein in the target cells occurs predominantly from specificity of transfection provided by the gene delivery vehicle, cell-type or tissue-type expression due to the transcriptional regulatory sequences controlling expression of the receptor gene, or a combination thereof. In other embodiments, initial delivery of the recombinant gene is more limited with introduction into the animal being quite localized. For example, the gene delivery vehicle can be introduced by catheter (see U.S. Patent 5,328,470) or by Stereotactic injection (*e.g.* Chen *et al.* (1994) *PNAS* 91: 3 054-3 05 7). The pharmaceutical preparation of the gene therapy construct can consist essentially of the gene delivery system in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Where the albumin fusion protein can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can comprise one or more cells which produce the

albumin fusion protein.

***Additional Gene Therapy Methods***

**[0557]** Also encompassed by the invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of an albumin fusion protein of the invention. This method requires a polynucleotide which codes for an albumin fusion protein of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the fusion protein by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

**[0558]** Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide encoding an albumin fusion protein of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the fusion protein of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

**[0559]** As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

**[0560]** In one embodiment, polynucleotides encoding the albumin fusion proteins of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, polynucleotides encoding the albumin fusion proteins of the present invention can also be delivered in liposome formulations and

lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

**[0561]** The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

**[0562]** Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the gene corresponding to the Therapeutic protein portion of the albumin fusion proteins of the invention.

**[0563]** Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

**[0564]** The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells.

They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

**[0565]** For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

**[0566]** The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

**[0567]** The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

**[0568]** The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

**[0569]** In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein

incorporated by reference), in functional form.

**[0570]** Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

**[0571]** Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

**[0572]** Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

**[0573]** For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15 degrees celcius. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

**[0574]** The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles

(SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include $Ca^{2+}$-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell 17:77 (1979)); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun. 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. 255:10431 (1980); Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA 75:145 (1978); Schaefer-Ridder et al., Science 215:166 (1982)), which are herein incorporated by reference.

**[0575]** Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

**[0576]** U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

**[0577]** In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding an albumin fusion protein of the present

invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

**[0578]** The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

**[0579]** The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding an albumin fusion protein of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a fusion protin of the present invention.

**[0580]** In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses fusion protein of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al. Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

**[0581]** Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224,

which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

**[0582]** Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

**[0583]** In certain other embodiments, the cells are engineered, ex vivo or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

**[0584]** For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a fusion protein of the invention.

**[0585]** Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present

invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), which are herein encorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

**[0586]** Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

**[0587]** The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

**[0588]** The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

**[0589]** The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

**[0590]** The polynucleotide encoding an albumin fusion protein of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at

the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

**[0591]** Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

**[0592]** A preferred method of local administration is by direct injection. Preferably, an albumin fusion protein of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

**[0593]** Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

**[0594]** Therapeutic compositions useful in systemic administration, include fusion proteins of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising albumin fusion proteins of the invention for targeting the vehicle to a particular site.

**[0595]** Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a

polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

**[0596]** Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

**[0597]** Albumin fusion proteins of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

***Biological Activities***

**[0598]** Albumin fusion proteins and/or polynucleotides encoding albumin fusion proteins of the present invention, can be used in assays to test for one or more biological activities. If an albumin fusion protein and/or polynucleotide exhibits an activity in a particular assay, it is likely that the Therapeutic protein corresponding to the fusion portein may be involved in the diseases associated with the biological activity. Thus, the fusion protein could be used to treat the associated disease.

**[0599]** In preferred embodiments, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indication Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired an albumin fusion protein of the invention that comprises a Therapeutic protein portion corresponding to a Therapeutic protein disclosed in the "Therapeutic Protein X" column of Table 1 (in the same row as the disease or disorder to be treated is listed in the "Preferred Indication Y" column of Table 1) in an amount effective to treat, prevent or ameliorate the disease or disorder.

**[0600]** In a further preferred embodiment, the present invention encompasses a method of treating a disease or disorder listed for a particular Therapeutic protein in the "Preferred Indication:Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired an albumin fusion protein of the invention that comprises a

Therapeutic protein portion corresponding to the Therapeutic protein for which the indications in the Examples are related in an amount effective to treat, prevent or ameliorate the disease or disorder.

**[0601]** Specifically contemplated by the present invention are albumin fusion proteins produced by a cell when encoded by the polynucleotides that encode SEQ ID NO:Y. When these polynucleotides are used to express the encoded protein from a cell, the cell's natural secretion and processing steps produces a protein that lacks the signal sequence explicitly listed in columns 4 and/or 11 of Table 2. The specific amino acid sequence of the listed signal sequence is shown in the specification or is well known in the art. Thus, most preferred embodiments of the present invention include the albumin fusion protein produced by a cell (which would lack the leader sequence shown in columns 4 and/or 11 of Table 2). Also most preferred are polypeptides comprising SEQ ID NO:Y without the specific leader sequence listed in columns 4 and/or 11 of Table 2. Compositions comprising these two preferred embodiments, including pharmaceutical compositions, are also preferred. These albumin fusion proteins are specifically contemplated to treat, prevent, or ameliorate a disease or disorder listed for a particular Therapeutic protein in the "Preferred Indication:Y" column of Table 1.

**[0602]** In preferred embodiments, fusion proteins of the present invention may be used in the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders relating to diseases and disorders of the endocrine system (see, for example, "Endocrine Disorders" section below), the nervous system (see, for example, "Neurological Disorders" section below), the immune system (see, for example, "Immune Activity" section below), respiratory system (see, for example, "Respiratory Disorders" section below), cardiovascular system (see, for example, "Cardiovascular Disorders" section below), reproductive system (see, for example, "Reproductive System Disorders" section below) digestive system (see, for example, "Gastrointestinal Disorders" section below), diseases and/or disorders relating to cell proliferation (see, for example, "Hyperproliferative Disorders" section below), and/or diseases or disorders relating to the blood (see, for example, "Blood-Related Disorders" section below).

**[0603]** In certain embodiments, an albumin fusion protein of the present invention may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the gene corresponding to the Therapeutic protein portion of the fusion protein of the invention is expressed.

**[0604]** Thus, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention are useful in the diagnosis, detection and/or treatment of diseases and/or

disorders associated with activities that include, but are not limited to, prohormone activation, neurotransmitter activity, cellular signaling, cellular proliferation, cellular differentiation, and cell migration.

**[0605]** More generally, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may be useful for the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders associated with the following systems.

***Immune Activity***

**[0606]** Albumin fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as a marker or detector of a particular immune system disease or disorder.

**[0607]** In another embodiment, a fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed.

**[0608]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass

deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

**[0609]** In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0610]** Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

**[0611]** In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0612]** Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

**[0613]** In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0614]** In a preferred embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

**[0615]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

**[0616]** Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

**[0617]** Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

**[0618]** Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the albumin fusion proteins of the invention

and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

**[0619]** Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

**[0620]** In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0621]** In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0622]** In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0623]** In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

**[0624]** In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a immunosuppressive agent(s).

**[0625]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

**[0626]** Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

**[0627]** Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin

fusion proteins of the invention, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate IgE concentrations in vitro or in vivo.

**[0628]** Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

**[0629]** Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis,

lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myosititis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

**[0630]** In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

**[0631]** In other embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

**[0632]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

**[0633]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, albumin fusion proteins of the

invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance tumor-specific immune responses.

**[0634]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

**[0635]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

**[0636]** In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

**[0637]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a

parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

**[0638]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

**[0639]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

**[0640]** In one embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

**[0641]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a stimulator of B cell responsiveness to pathogens.

**[0642]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an activator of T cells.

**[0643]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

**[0644]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to induce higher affinity antibodies.

**[0645]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to increase serum immunoglobulin concentrations.

**[0646]** In another specific embodiment, albumin fusion proteins of the invention and/or

polynucleotides encoding albumin fusion proteins of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

**[0647]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

**[0648]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

**[0649]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

**[0650]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

**[0651]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, albumin

fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention enhance antigen presentation or antagonize antigen presentation in vitro or in vivo. Moreover, in related embodiments, this enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

**[0652]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

**[0653]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

**[0654]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

**[0655]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used in the pretreatment of bone marrow samples prior to transplant.

**[0656]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

**[0657]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

**[0658]** In another specific embodiment, albumin fusion proteins of the invention and/or

polynucleotides encoding albumin fusion proteins of the invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

**[0659]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used in one or more of the applications decribed herein, as they may apply to veterinary medicine.

**[0660]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

**[0661]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

**[0662]** In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

**[0663]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

**[0664]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

**[0665]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin

fusion proteins of the invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

**[0666]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to enhance or inhibit complement mediated cell lysis.

**[0667]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

**[0668]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

**[0669]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be employed to treat adult respiratory distress syndrome (ARDS).

**[0670]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to stimulate the regeneration of mucosal surfaces.

**[0671]** In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented,

diagnosed, prognosed, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

**[0672]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

**[0673]** In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

**[0674]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

**[0675]** In another specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

**[0676]** In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

***Blood-Related Disorders***

**[0677]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used to treat or prevent blood coagulation diseases, disorders, and/or

conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

**[0678]** In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

**[0679]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed.

**[0680]** The fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion

proteins of the invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

**[0681]** The fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to prevent, treat, or diagnose blood dyscrasia.

**[0682]** Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

**[0683]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease,

hemoglobin S-C disease, and hemoglobin E disease). Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to, major and minor forms of alpha-thalassemia and beta-thalassemia.

**[0684]** In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

**[0685]** The effect of the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

**[0686]** Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

**[0687]** In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to,

neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

**[0688]** Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

**[0689]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited to, lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia

telangiectsia).

**[0690]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

**[0691]** In another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

**[0692]** In yet another embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphpblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

**[0693]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

**[0694]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and seconday thrombocythemia) and chronic myelocytic leukemia.

**[0695]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as a treatment

prior to surgery, to increase blood cell production.

**[0696]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosionophils and macrophages.

**[0697]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

**[0698]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as an agent to increase cytokine production.

**[0699]** In other embodiments, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

***Hyperproliferative Disorders***

**[0700]** In certain embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may proliferate other cells which can inhibit the hyperproliferative disorder.

**[0701]** For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

**[0702]** Examples of hyperproliferative disorders that can be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention

include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

**[0703]** Similarly, other hyperproliferative disorders can also be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma,

Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

**[0704]** In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

**[0705]** Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

**[0706]** Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

**[0707]** Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin

dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

**[0708]** Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

**[0709]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed.

**[0710]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to, those described herein. In a further preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

**[0711]** Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or

agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

**[0712]** In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

**[0713]** Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma,

ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

**[0714]** Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

**[0715]** Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

**[0716]** Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

**[0717]** Another preferred embodiment utilizes polynucleotides encoding albumin fusion proteins of the invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

**[0718]** Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide encoding an albumin fusion

protein of the present invention, wherein said polynucleotide represses said expression.

**[0719]** Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the fusion protein of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

**[0720]** Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

**[0721]** For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references

are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

**[0722]** The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

**[0723]** By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

**[0724]** Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

**[0725]** Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference).

**[0726]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion

proteins of the invention may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. These fusion protieins and/or polynucleotides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, these fusion proteins and/or polynucleotides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of these proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

**[0727]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering these albumin fusion proteins and/or polynucleotides, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

**[0728]** In another embodiment, the invention provides a method of delivering compositions containing the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to targeted cells expressing the a polypeptide bound by, that binds to, or associates with an albumin fuison protein of the invention. Albumin fusion proteins of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

**[0729]** Albumin fusion proteins of the invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the albumin fusion proteins of the invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and

immunogens.

***Renal Disorders***

**[0730]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

**[0731]** Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

**[0732]** In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

**[0733]** Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

**[0734]** Compositions of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Compositions of the invention may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides of the invention are described in more detail herein.

***Cardiovascular Disorders***

**[0735]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

**[0736]** Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

**[0737]** Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive

cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

**[0738]** Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

**[0739]** Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

**[0740]** Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

**[0741]** Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

**[0742]** Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension,

ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

**[0743]** Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

**[0744]** Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

**[0745]** Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

**[0746]** Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

**[0747]** Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

**[0748]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots,

other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Methods of delivering polynucleotides are described in more detail herein.

***Respiratory Disorders***

**[0749]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

**[0750]** Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

**[0751]** Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration

pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthsma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

***Anti-Angiogenesis Activity***

**[0752]** The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell 56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech. 9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.,* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

**[0753]** The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of fusion proteins of the invention and/or polynucleotides

encoding albumin fusion proteins of the invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention. For example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

**[0754]** Within yet other aspects, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

**[0755]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental

fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

**[0756]** For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to a hypertrophic scar or keloid.

**[0757]** Within one embodiment of the present invention fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

**[0758]** Moreover, Ocular disorders associated with neovascularization which can be treated with the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al., Surv. Ophthal. 22*:291-312 (1978).

**[0759]** Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (e.g., fusion proteins of the invention and/or polynucleotides encoding

albumin fusion proteins of the invention) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

**[0760]** Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

**[0761]** Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per

year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

**[0762]** Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eyes, such that the formation of blood vessels is inhibited.

**[0763]** Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

**[0764]** Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of an albumin fusion protein of the invention and/or polynucleotides encoding an albumin fusion protein of the invention to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

**[0765]** Additionally, disorders which can be treated with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

**[0766]** Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the albumin fusion proteins of the invention and/or polynucleotides encoding

albumin fusion proteins of the invention of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

**[0767]** In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

**[0768]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

**[0769]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may

be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

**[0770]** Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

**[0771]** Within one aspect of the present invention, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

**[0772]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

**[0773]** Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

**[0774]** Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and

orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

**[0775]** Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

**[0776]** A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, (1992)); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

***Diseases at the Cellular Level***

[0777] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0778] In preferred embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

[0779] Additional diseases or conditions associated with increased cell survival that could be treated or detected by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's

tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

**[0780]** Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognesed using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

***Wound Healing and Epithelial Cell Proliferation***

**[0781]** In accordance with yet a further aspect of the present invention, there is provided a process for utilizing fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to promote dermal reestablishment subsequent to dermal loss

**[0782]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to increase the adherence of skin grafts to a wound bed

and to stimulate re-epithelialization from the wound bed. The following are types of grafts that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to promote skin strength and to improve the appearance of aged skin.

**[0783]** It is believed that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

**[0784]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may have a cytoprotective effect on the small intestine mucosa. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

**[0785]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying

dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to treat diseases associate with the under expression.

**[0786]** Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to prevent and heal damage to the lungs due to various pathological states. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

**[0787]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

**[0788]** In addition, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

*Neural Activity and Neurological Diseases*

**[0789]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or

disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

**[0790]** In one embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

**[0791]** In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

**[0792]** In another preferred embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

**[0793]** The compositions of the invention which are useful for treating or preventing a nervous

system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, *10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, *70*:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, *4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

**[0794]** In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

**[0795]** Further, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may

also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

**[0796]** Additionally, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

**[0797]** In accordance with yet a further aspect of the present invention, there is provided a process for utilizing fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used to treat and/or detect neurologic diseases. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

**[0798]** Examples of neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms,

hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

**[0799]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

**[0800]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

**[0801]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include

hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

**[0802]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

**[0803]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome,

De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

**[0804]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such

as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

**[0805]** Additional neurologic diseases which can be treated or detected with fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

***Endocrine Disorders***

**[0806]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose disorders

and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

**[0807]** Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

**[0808]** Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

**[0809]** Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

**[0810]** In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia),

congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

**[0811]** Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

**[0812]** In another embodiment, albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the Therapeutic protein corresponding to the Therapeutic protein portion of the albumin protein of the invention is expressed,

***Reproductive System Disorders***

**[0813]** The albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

**[0814]** Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

**[0815]** Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

**[0816]** Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

**[0817]** Moreover, diseases and/or disorders of the vas deferens include vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

**[0818]** Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

**[0819]** Further, the polynucleotides, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

**[0820]** Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine

polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

**[0821]** Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

**[0822]** Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

**[0823]** Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis,

cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

**[0824]** Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

**[0825]** Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

**[0826]** Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

***Infectious Disease***

**[0827]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

**[0828]** Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae,

Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat AIDS.

**[0829]** Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*, *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g.,

*Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae and Mycobacterium tuberculosis)*, Vibrio (e.g., *Vibrio cholerae)*, Neisseriaceae (e.g., *Neisseria gonorrhea, Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningiococcus, Pneumococcus and Streptococcus (e.g., *Streptococcus pneumoniae* and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., mengitis types A and B), chlamydia, syphillis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

**[0830]** Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardias, Helminthiasis, Leishmaniasis, Schistisoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparium*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety

of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention are used to treat, prevent, and/or diagnose malaria.

**[0831]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could either be by administering an effective amount of an albumin fusion protein of the invention to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

***Regeneration***

**[0832]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

**[0833]** Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

**[0834]** Moreover, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other

tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

**[0835]** Similarly, nerve and brain tissue could also be regenerated by using fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention.

***Gastrointestinal Disorders***

**[0836]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

**[0837]** Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

**[0838]** Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine,

lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

**[0839]** Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

**[0840]** Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

**[0841]** Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

**[0842]** Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer,

gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

**[0843]** Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

***Chemotaxis***

**[0844]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

**[0845]** Albumin fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present

invention can also attract fibroblasts, which can be used to treat wounds.

**[0846]** It is also contemplated that fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, fusion proteins of the invention and/or polynucleotides encoding albumin fusion proteins of the invention could be used as an inhibitor of chemotaxis.

***Binding Activity***

**[0847]** Albumin fusion proteins of the invention may be used to screen for molecules that bind to the Therapeutic protein portion of the fusion protein or for molecules to which the Therapeutic protein portion of the fusion protein binds. The binding of the fusion protein and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the fusion protein or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

**[0848]** Preferably, the molecule is closely related to the natural ligand of the Therapeutic protein portion of the fusion protein of the invention, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the Therapeutic protein portion of an albumin fusion protein of the invention binds, or at least, a fragment of the receptor capable of being bound by the Therapeutic protein portion of an albumin fusion protein of the invention (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

**[0849]** Preferably, the screening for these molecules involves producing appropriate cells which express the albumin fusion proteins of the invention. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*.

**[0850]** The assay may simply test binding of a candidate compound to an albumin fusion protein of the invention, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the fusion protein.

**[0851]** Alternatively, the assay can be carried out using cell-free preparations, fusion protein/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing an albumin fusion protein, measuring fusion protein/molecule activity or binding, and comparing the fusion protein/molecule activity or binding to a standard.

**[0852]** Preferably, an ELISA assay can measure fusion protein level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure fusion protein level or activity by either binding, directly or indirectly, to the albumin fusion protein or by competing with the albumin fusion protein for a substrate.

**[0853]** Additionally, the receptor to which a Therapeutic protein portion of an albumin fusion protein of the invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, in cases wherein the Therapeutic protein portion of the fusion protein corresponds to FGF, expression cloning may be employed wherein polyadenylated RNA is prepared from a cell responsive to the albumin fusion protein, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the albumin fusion protein. Transfected cells which are grown on glass slides are exposed to the albumin fusion protein of the present invention, after they have been labeled. The albumin fusion proteins can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

**[0854]** Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

**[0855]** As an alternative approach for receptor identification, a labeled albumin fusion protein can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule for the Therapeutoc protein component of an albumin fusion protein of the invention, the linked material may be resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the fusion protein can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

**[0856]** Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the fusion protein, and/or Therapeutic protein portion or albumin component of an albumin fusion protein of the present invention, thereby effectively generating agonists and

antagonists of an albumin fusion protein of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides encoding albumin fusion proteins of the invention and thus, the albumin fusion proteins encoded thereby, may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides encoding albumin fusion proteins of the invention and thus, the albumin fusion proteins encoded thereby, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of an albumin fusion protein of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

**[0857]** Other preferred fragments are biologically active fragments of the Therapeutic protein portion and/or albumin component of the albumin fusion proteins of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a Therapeutic protein portion and/or albumin component of the albumin fusion proteins of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

**[0858]** Additionally, this invention provides a method of screening compounds to identify those which modulate the action of an albumin fusion protein of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, an albumin fusion protein of the present invention, and the compound to be screened and $^{3}$[H] thymidine under cell culture

conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of $^{3}$[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of $^{3}$[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

**[0859]** In another method, a mammalian cell or membrane preparation expressing a receptor for the Therapeutic protien component of a fusion protine of the invention is incubated with a labeled fusion protein of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential fusion protein. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

**[0860]** All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the fusion protein/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the albumin fusion proteins of the invention from suitably manipulated cells or tissues.

**[0861]** Therefore, the invention includes a method of identifying compounds which bind to an albumin fusion protein of the invention comprising the steps of: (a) incubating a candidate binding compound with an albumin fusion protein of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with an albumin fusion protein of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the fusion protein has been altered.

***Targeted Delivery***

**[0862]** In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a component of an albumin fusion protein of the invention.

**[0863]** As discussed herein, fusion proteins of the invention may be associated with heterologous

polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering fusion proteins of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a Therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

**[0864]** In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering an albumin fusion protein of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

**[0865]** By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

***Drug Screening***

**[0866]** Further contemplated is the use of the albumin fusion proteins of the present invention, or the polynucleotides encoding these fusion proteins, to screen for molecules which modify the activities of the albumin fusion protein of the present invention or proteins corresponding to the Therapeutic protein portion of the albumin fusion protein. Such a method would include contacting the fusion protein with a selected compound(s) suspected of having antagonist or

agonist activity, and assaying the activity of the fusion protein following binding.

**[0867]** This invention is particularly useful for screening therapeutic compounds by using the albumin fusion proteins of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The albumin fusion protein employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the albumin fusion protein. Drugs are screened against such transformed cells or supernatants obtained from culturing such cells, in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and an albumin fusion protein of the present invention.

**[0868]** Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the albumin fusion proteins of the present invention. These methods comprise contacting such an agent with an albumin fusion protein of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the albumin fusion protein or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the albumin fusion protein of the present invention.

**[0869]** Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to an albumin fusion protein of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with an albumin fusion protein of the present invention and washed. Bound peptides are then detected by methods well known in the art. Purified albumin fusion protein may be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

**[0870]** This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding an albumin fusion protein of the present invention specifically compete with a test compound for binding to the albumin fusion protein or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares

one or more antigenic epitopes with an albumin fusion protein of the invention.

***Binding Peptides and Other Molecules***

**[0871]** The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind albumin fusion proteins of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the albumin fusion proteins of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

**[0872]** This method comprises the steps of: contacting an albumin fusion protein of the invention with a plurality of molecules; and identifying a molecule that binds the albumin fusion protein.

**[0873]** The step of contacting the albumin fusion protein of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the albumin fusion protein on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized albumin fusion protein of the invention. The molecules having a selective affinity for the albumin fusion protein can then be purified by affinity selection. The nature of the solid support, process for attachment of the albumin fusion protein to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

**[0874]** Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by an albumin fusion protein of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the albumin fusion protein and the individual clone. Prior to contacting the albumin fusion protein with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a

DNA construct encoding a polypeptide having a selective affinity for an albumin fusion protein of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for an albumin fusion protein of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

**[0875]** In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of an albumin fusion protein of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the albumin fusion protein of the invention or the plurality of polypeptides are bound to a solid support.

**[0876]** The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind an albumin fusion protein of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and *in vitro* translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., Science 251:767-773 (1991); Houghten et al., Nature 354:84-86 (1991); Lam et al., Nature 354:82-84 (1991); Medynski, Bio/Technology 12:709-710 (1994); Gallop et al., J. Medicinal Chemistry 37(9):1233-1251 (1994); Ohlmeyer et al., Proc. Natl. Acad. Sci. USA 90:10922-10926 (1993); Erb et al., Proc. Natl. Acad. Sci. USA 91:11422-11426 (1994); Houghten et al., Biotechniques 13:412 (1992); Jayawickreme et al., Proc. Natl. Acad. Sci. USA 91:1614-1618 (1994); Salmon et al., Proc. Natl. Acad. Sci. USA 90:11708-11712 (1993); PCT Publication No. WO 93/20242; and Brenner and Lerner, Proc. Natl. Acad. Sci. USA 89:5381-5383 (1992).

**[0877]** Examples of phage display libraries are described in Scott et al., Science 249:386-390 (1990); Devlin et al., Science, 249:404-406 (1990); Christian et al., 1992, J. Mol. Biol. 227:711-718 1992); Lenstra, J. Immunol. Meth. 152:149-157 (1992); Kay et al., Gene 128:59-65 (1993); and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

**[0878]** In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., Proc. Natl. Acad. Sci. USA 91:9022-9026 (1994).

**[0879]** By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et

al., Proc. Natl. Acad. Sci. USA 91:4708-4712 (1994)) can be adapted for use. Peptoid libraries (Simon et al., Proc. Natl. Acad. Sci. USA 89:9367-9371 (1992)) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (Proc. Natl. Acad. Sci. USA 91:11138-11142 (1994)).

**[0880]** The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke (Bio/Technology 13:351-360 (1995) list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

**[0881]** Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

**[0882]** Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

**[0883]** Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley et al., Adv. Exp. Med. Biol. 251:215-218 (1989); Scott et al,. Science 249:386-390 (1990); Fowlkes et al., BioTechniques 13:422-427 (1992); Oldenburg et al., Proc. Natl. Acad. Sci. USA 89:5393-5397 (1992); Yu et al., Cell 76:933-945 (1994); Staudt et al., Science 241:577-580 (1988); Bock et al., Nature 355:564-566 (1992); Tuerk et al., Proc. Natl. Acad. Sci. USA 89:6988-6992 (1992); Ellington et al., Nature 355:850-852 (1992); U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar et al., Science 263:671-673 (1993); and PCT Publication No. WO 94/18318.

**[0884]** In a specific embodiment, screening to identify a molecule that binds an albumin fusion protein of the invention can be carried out by contacting the library members with an albumin

fusion protein of the invention immobilized on a solid phase and harvesting those library members that bind to the albumin fusion protein. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley et al., Gene 73:305-318 (1988); Fowlkes et al., BioTechniques 13:422-427 (1992); PCT Publication No. WO 94/18318; and in references cited herein.

**[0885]** In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields et al., Nature 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA 88:9578-9582 (1991) can be used to identify molecules that specifically bind to polypeptides of the invention.

**[0886]** Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

**[0887]** Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

**[0888]** As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

**[0889]** The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

***Other Activities***

**[0890]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The albumin fusion proteins of the invention and/or

polynucleotides encoding albumin fusion proteins of the invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

**[0891]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

**[0892]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

**[0893]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

**[0894]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for preventing hair loss. Along the same lines, an albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

**[0895]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

**[0896]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

**[0897]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be used to modulate mammalian characteristics, such as

body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, an albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

**[0898]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

**[0899]** An albumin fusion protein of the invention and/or polynucleotide encoding an albumin fusion protein of the invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

**[0900]** The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

**[0901]** Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

**[0902]** Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the alterations detected in the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

## EXAMPLES

### *EXAMPLE 1: Generation of pScNHSA and pScCHSA.*

**[0903]** The vectors pScNHSA (ATCC Deposit No. PTA-3279) and pScCHSA (ATCC Deposit

No. PTA-3276) are derivatives of pPPC0005 (ATCC Deposit No. PTA-3278) and are used as cloning vectors into which polynucleotides encoding a therapeutic protein or fragment or variant thereof is inserted adjacent to and in translation frame with polynucleotides encoding human serum albumin "HSA". pScCHSA may be used for generating Therapeutic protein-HSA fusions, while pScNHSA may be used to generate HSA-Therapeutic protein fusions.

*Generation of pScCHSA: albumin fusion with the albumin moiety C-terminal to the therapeutic portion.*

**[0904]** A vector to facilitate cloning DNA encoding a Therapeutic protein N-terminal to DNA encoding the mature albumin protein was made by altering the nucleic acid sequence that encodes the chimeric HSA signal peptide in pPPC0005 to include the *Xho* I and *Cla* I restriction sites.

**[0905]** First, the *Xho* I and *Cla* I sites inherent to pPPC0005 (located 3' of the ADH1 terminator sequence) were eliminated by digesting pPPC0005 with *Xho* I and *Cla* I, filling in the sticky ends with T4 DNA polymerase, and religating the blunt ends to create pPPC0006.

**[0906]** Second, the *Xho* I and *Cla* I restriction sites were engineered into the nucleic acid sequence that encodes the signal peptide of HSA (a chimera of the HSA leader and a kex2 site from mating factor alpha, "MAF") in pPPC0006 using two rounds of PCR. In the first round of PCR, amplification with primers shown as SEQ ID NO:36 and SEQ ID NO:37 was performed. The primer whose sequence is shown as SEQ ID NO:36 comprises a nucleic acid sequence that encodes part of the signal peptide sequence of HSA, a kex2 site from the mating factor alpha leader sequence, and part of the amino-terminus of the mature form of HSA. Four point mutations were introduced in the sequence, creating the *Xho* I and *Cla* I sites found at the junction of the chimeric signal peptide and the mature form of HSA. These four mutations are underlined in the sequence shown below. In pPPC0005 the nucleotides at these four positions from 5' to 3' are T, G, T, and G.

5'-GCCTCGAGAAAAGAGATGCACACAAGAGTGAGGTTGCTCATCGATTTAAAGATTT GGG-3' (SEQ ID NO:36) and

5'-AATCGATGAGCAACCTCACTCTTGTGTGCATCTCTTTTCTCGAGGCTCCTGGAATA AGC-3' (SEQ ID NO:37). A second round of PCR was then performed with an upstream flanking primer, 5'-TACAAACTTAAGAGTCCAATTAGC-3' (SEQ ID NO:38) and a downstream flanking primer 5'-CACTTCTCTAGAGTGGTTTCATATGTCTT-3' (SEQ ID NO:39). The resulting PCR product was then purified and digested with *Afl* II and *Xba* I and ligated into the same sites in pPPC0006 creating pScCHSA. The resulting plasmid has *Xho* I and *Cla* I sites engineered into the signal sequence. The presence of the *Xho* I site creates a single

amino acid change in the end of the signal sequence from LDKR to LEKR. The D to E change will not be present in the final albumin fusion protein expression plasmid when a nucleic acid sequence comprising a polynucleotide encoding the Therapeutic portion of the albumin fusion protein with a 5' *Sal* I site (which is compatible with the *Xho* I site) and a 3' *Cla* I site is ligated into the *Xho* I and *Cla* I sites of pScCHSA. Ligation of *Sal* I to *Xho* I restores the original amino acid sequence of the signal peptide sequence. DNA encoding the Therapeutic portion of the albumin fusion protein may be inserted after the Kex2 site (Kex2 cleaves after the dibasic amino acid sequence KR at the end of the signal peptide) and prior to the *Cla* I site.

*Generation of pScNHSA: albumin fusion with the albumin moiety N-terminal to the therapeutic portion.*

**[0907]** A vector to facilitate cloning DNA encoding a Therapeutic protein portion C-terminal to DNA encoding the mature albumin protein, was made by adding three, eight-base-pair restriction sites to pScCHSA. The *Asc* I, *Fse* I, and *Pme* I restriction sites were added in between the *Bsu36* I and *Hind* III sites at the end of the nucleic acid sequence encoding the mature HSA protein. This was accomplished through the use of two complementary synthetic primers containing the *Asc* I, *Fse* I, and *Pme* I restriction sites underlined (SEQ ID NO:40 and SEQ ID NO:41). 5'-AAGCTGCCTTAGGCTTATAATAAGGCGCGCCGGCCGGCCGTTTAAACTAAGCTTA ATTCT-3' (SEQ ID NO:40) and 5-AGAATTAAGCTTAGTTTAAACGGCCGGCCGGCGCGCCTTATTATAAGCCTAAGGCA GCTT-3' (SEQ ID NO:41). These primers were annealed and digested with *Bsu36* I and *Hind* III and ligated into the same sites in pScCHSA creating pScNHSA.

***EXAMPLE 2: General Construct Generation for Yeast Transformation.***

**[0908]** The vectors pScNHSA and pScCHSA may be used as cloning vectors into which polynucleotides encoding a therapeutic protein or fragment or variant thereof is inserted adjacent to polynucleotides encoding mature human serum albumin "HSA". pScCHSA is used for generating Therapeutic protein-HSA fusions, while pScNHSA may be used to generate HSA-Therapeutic protein fusions.

*Generation of albumin fusion constructs comprising HSA-Therapeutic protein fusion products.*

**[0909]** DNA encoding a Therapeutic protein (e.g., sequences shown in SEQ ID NO:X or known in the art) may be PCR amplified using the primers which facilitate the generation of a fusion construct (e.g., by adding restriction sites, encoding seamless fusions, encoding linker sequences, etc.) For example, one skilled in the art could design a 5' primer that adds polynucleotides

encoding the last four amino acids of the mature form of HSA (and containing the *Bsu*36I site) onto the 5' end of DNA encoding a Therapeutic protein; and a 3' primer that adds a STOP codon and appropriate cloning sites onto the 3' end of the Therapeutic protein coding sequence. For instance, the forward primer used to amplify DNA encoding a Therapeutic protein might have the sequence, 5'-aagctGCCTTAGGCTTA$(N)_{15}$-3' (SEQ ID NO:42) where the underlined sequence is a *Bsu*36I site, the upper case nucleotides encode the last four amino acids of the mature HSA protein (ALGL), and $(N)_{15}$ is identical to the first 15 nucleotides encoding the Therapetic protein of interest. Similarly, the reverse primer used to amplify DNA encoding a Therapeutic protein might have the sequence, 5'-GCGCGC*GTTTAAAC*GGCCGGCCGGCGCGCCTTATTA$(N)_{15}$-3' (SEQ ID NO:43) where the italicized sequence is a *Pme* I site, the double underlined sequence is an *Fse* I site, the singly underlined sequence is an *Asc* I site, the boxed nucleotides are the reverse complement of two tandem stop codons, and $(N)_{15}$ is identical to the reverse complement of the last 15 nucleotides encoding the Therapeutic protein of interest. Once the PCR product is amplified it may be cut with *Bsu*36I and one of (*Asc* I, *Fse* I, or *Pme* I) and ligated into pScNHSA.

**[0910]** The presence of the *Xho* I site in the HSA chimeric leader sequence creates a single amino acid change in the end of the chimeric signal sequence, i.e. the HSA-kex2 signal sequence, from LDKR (SEQ ID NO:44) to LEKR (SEQ ID NO:45).

*Generation of albumin fusion constructs comprising gene-HSA fusion products.*

**[0911]** Similar to the method described above, DNA encoding a Therapeutic protein may be PCR amplified using the following primers: A 5' primer that adds polynucleotides containing a *SalI* site and encoding the last three amino acids of the HSA leader sequence, DKR, onto the 5' end of DNA encoding a Therapeutic protein; and a 3' primer that adds polynucleotides encoding the first few amino acids of the mature HSA containing a *Cla* I site onto the 3' end of DNA encoding a Therapeutic protein. For instance, the forward primer used to amplify the DNA encoding a Therapeutic protein might have the sequence, 5'-aggagcgtcGACAAAAGA$(N)_{15}$-3' (SEQ ID NO:46) where the underlined sequence is a *Sal* I site, the upper case nucleotides encode the last three amino acids of the HSA leader sequence (DKR), and $(N)_{15}$ is identical to the first 15 nucleotides encoding the Therapetic protein of interest. Similarly, the reverse primer used to amplify the DNA encoding a Therapeutic protein might have the sequence, 5'-CTTTAA*ATCGAT*GAGCAACCTCACTCTTGTGTGCATC$(N)_{15}$-3'(SEQ ID NO:47) where the italicized sequence is a *Cla* I site, the underlined nucleotides are the reverse complement of the DNA encoding the first 9 amino acids of the mature form of HSA (DAHKSEVAH, SEQ ID

NO:48), and $(N)_{15}$ is identical to the reverse complement of the last 15 nucleotides encoding the Therapeutic protein of interest. Once the PCR product is amplified it may be cut with *Sal* I and *Cla* I and ligated into pScCHSA digested with *Xho* I and *Cla* I. A different signal or leader sequence may be desired, for example, invertase "INV" (Swiss-Prot Accession P00724), mating factor alpha "MAF" (Genbank Accession AAA18405), MPIF (Geneseq AAF82936), Fibulin B (Swiss-Prot Accession P23142), Clusterin (Swiss-Prot Accession P10909), Insulin-Like Growth Factor- Binding Protein 4 (Swiss-Prot Accession P22692), and permutations of the HSA leader sequence can be subcloned into the appropriate vector by means of standard methods known in the art.

*Generation of albumin fusion construct compatible for expression in yeast S. cerevisiae.*

**[0912]** The *Not* I fragment containing the DNA encoding either an N-terminal or C-terminal albumin fusion protein generated from pScNHSA or pScCHSA may then be cloned into the *Not* I site of pSAC35 which has a LEU2 selectable marker. The resulting vector is then used in transformation of a yeast *S. cerevisiae* expression system.

***EXAMPLE 3: General Expression in Yeast S. cerevisiae.***

**[0913]** An expression vector compatible with yeast expression can be transformed into yeast *S. cerevisiae* by lithium acetate transformation, electroporation, or other methods known in the art and or as described in part in Sambrook, Fritsch, and Maniatis. 1989. "Molecular Cloning: A Laboratory Manual, 2nd edition", volumes 1-3, and in Ausubel et al. 2000. Massachusetts General Hospital and Harvard Medical School "Current Protocols in Molecular Biology", volumes 1-4. The expression vectors are introduced into *S. cerevisiae* strains DXY1, D88, or BXP10 by transformation, individual transformants can be grown, for example, for 3 days at 30°C in 10 mL YEPD (1% w/v yeast extract, 2 % w/v, peptone, 2 % w/v, dextrose), and cells can be collected at stationary phase after 60 hours of growth. Supernatants are collected by clarifying cells at 3000g for 10 minutes.

**[0914]** pSAC35 (Sleep et al., 1990, Biotechnology 8:42 and see Figure 3) comprises, in addition to the LEU2 selectable marker, the entire yeast 2 μm plasmid to provide replication functions, the PRB1 promoter, and the ADH1 termination signal.

***EXAMPLE 4: General Purification of an Albumin Fusion Protein Expressed from an Albumin Fusion in Yeast S. cerevisiae.***

**[0915]** In preferred embodiments, albumin fusion proteins of the invention comprise the mature form of HSA fused to either the N- or C- terminus of the mature form of a therapeutic protein or portions thereof (e.g., the mature form of a therapeutic protein listed in Table 1, or the mature

form of a therapeutic protein shown in Table 2 as SEQ ID NO:Z). In one embodiment of the invention, albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature albumin fusion protein is secreted directly into the culture medium. Albumin fusion proteins of the invention preferably comprise heterologous signal sequences (e.g., the non-native signal sequence of a particular therapeutic protein) including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. Especially preferred as those signal sequence listed in Table 2 and/or the signal sequence listed in the "Expression of Fusion Proteins" and/or "Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins" section of the specification, above. In preferred embodiments, the fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

**[0916]** Albumin fusion proteins expressed in yeast as described above can be purified on a small-scale over a Dyax peptide affinity column as follows. Supernatants from yeast expressing an albumin fusion protein is diafiltrated against 3 mM phosphate buffer pH 6.2, 20 mM NaCl and 0.01% Tween 20 to reduce the volume and to remove the pigments. The solution is then filtered through a 0.22 μm device. The filtrate is loaded onto a Dyax peptide affinity column. The column is eluted with 100 mM Tris/HCl, pH 8.2 buffer. The peak fractions containing protein are collected and analyzed on SDS-PAGE after concentrating 5-fold.

**[0917]** For large scale purification, the following method can be utilized. The supernatant in excess of 2 L is diafiltered and concentrated to 500 mL in 20 mM Tris/HCl pH 8.0. The concentrated protein solution is loaded onto a pre-equilibrated 50 mL DEAE-Sepharose Fast Flow column, the column is washed, and the protein is eluted with a linear gradient of NaCl from 0 to 0.4 M NaCl in 20 mM Tris/HCl, pH 8.0. Those fractions containing the protein are pooled, adjusted to pH 6.8 with 0.5 M sodium phosphate ($NaH_2PO_4$). A final concentration of 0.9 M $(NH_4)_2SO_4$ is added to the protein solution and the whole solution is loaded onto a pre-equilibrated 50 mL Butyl650S column. The protein is eluted with a linear gradient of ammonium sulfate (0.9 to 0 M $(NH_4)_2SO_4$). Those fractions with the albumin fusion are again pooled, diafiltered against 10 mM $Na_2HPO_4$/citric acid buffer pH 5.75, and loaded onto a 50 mL pre-equilibrated SP-Sepharose Fast Flow column. The protein is eluted with a NaCl linear gradient

from 0 to 0.5 M. The fractions containing the protein of interest are combined, the buffer is changed to 10 mM $Na_2HPO_4$/citric acid pH 6.25 with an Amicon concentrator, the conductivity is < 2.5 mS/cm. This protein solution is loaded onto a 15 mL pre-equilibrated Q-Sepharose high performance column, the column is washed, and the protein is eluted with a NaCl linear gradient from 0 to 0.15 M NaCl. The purified protein can then be formulated into a specific buffer composition by buffer exchange.

***EXAMPLE 5: General Construct Generation for Mammalian Cell Transfection.***

*Generation of albumin fusion construct compatible for expression in mammalian cell-lines.*

**[0918]** Albumin fusion constructs can be generated in expression vectors for use in mammalian cell culture systems. DNA encoding a therapeutic protein can be cloned N-terminus or C-terminus to HSA in a mammalian expression vector by standard methods known in the art (e.g., PCR amplification, restriction digestion, and ligation). Once the expression vector has been constructed, transfection into a mammalian expression system can proceed. Suitable vectors are known in the art including, but not limited to, for example, the pC4 vector, and/or vectors available from Lonza Biologics, Inc. (Portsmouth, NH).

**[0919]** The DNA encoding human serum albumin has been cloned into the pC4 vector which is suitable for mammalian culture systems, creating plasmid pC4:HSA (ATCC Deposit # PTA-3277). This vector has a DiHydroFolate Reductase, "DHFR", gene that will allow for selection in the presence of methotrexate.

**[0920]** The pC4:HSA vector is suitable for expression of albumin fusion proteins in CHO cells. For expression, in other mammalian cell culture systems, it may be desirable to subclone a fragment comprising, or alternatively consisting of, DNA which encodes for an albumin fusion protein into an alternative expression vector. For example, a fragment comprising, or alternatively consisting, of DNA which encodes for a mature albumin fusion protein may be subcloned into another expression vector including, but not limited to, any of the mammalian expression vectors described herein.

**[0921]** In a preferred embodiment, DNA encoding an albumin fusion construct is subcloned into vectors provided by Lonza Biologics, Inc. (Portsmouth, NH) by procedures known in the art for expression in NS0 cells.

*Generation of albumin fusion constructs comprising HSA-Therapeutic Protein fusion products.*

**[0922]** Using pC4:HSA (ATCC Deposit # PTA-3277), albumin fusion constructs can be

generated in which the Therapeutic protein portion is C terminal to the mature albumin sequence. For example, one can clone DNA encoding a Therapeutic protein of fragment or variant thereof between the *Bsu* 36I and *Asc* I restriction sites of the vector. When cloning into the *Bsu* 36I and *Asc* I, the same primer design used to clone into the yeast vector system (SEQ ID NO:42 and 43) may be employed (see Example 2).

*Generation of albumin fusion constructs comprising gene-HSA fusion products.*

**[0923]** Using pC4:HSA (ATCC Deposit # PTA-3277), albumin fusion constructs can be generated in which a Therapeutic protein portion is cloned N terminal to the mature albumin sequence. For example, one can clone DNA encoding a Therapeutic protein that has its own signal sequence between the *Bam* HI (or *Hind* III) and *Cla* I sites of pC4:HSA. When cloning into either the *Bam* HI or *Hind* III site, it is preferrable to include a Kozak sequence (CCGCCACCATG, SEQ ID NO:49) prior to the translational start codon of the DNA encoding the Therapeutic protein. If a Therapeutic protein does not have a signal sequence, DNA encoding that Therapeutic protein may be cloned in between the *Xho* I and *Cla* I sites of pC4:HSA. When using the *Xho* I site, the following 5' (SEQ ID NO:50) and 3' (SEQ ID NO:51) exemplary PCR primers may be used:

5'-CCGCCGCTCGAGGGGTGTGTTTCGTCGA$(N)_{18}$-3' (SEQ ID NO: 50)

5'-AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATC$(N)_{18}$-3' (SEQ ID NO:51)

**[0924]** In the 5' primer (SEQ ID NO:50), the underlined sequence is a *Xho* I site; and the *Xho* I site and the DNA following the *Xho* I site code for the last seven amino acids of the leader sequence of natural human serum albumin. In SEQ ID NO:50, "$(N)_{18}$" is DNA identical to the first 18 nucleotides encoding the Therapeutic protein of interest. In the 3' primer (SEQ ID NO:51), the underlined sequence is a *Cla* I site; and the *Cla* I site and the DNA following it are the reverse complement of the DNA encoding the first 10 amino acids of the mature HSA protein (SEQ ID NO:1). In SEQ ID NO:51 "$(N)_{18}$" is the reverse complement of DNA encoding the last 18 nucleotides encoding the Therapeutic protein of interest. Using these two primers, one may PCR amplify the Therapeutic protein of interest, purify the PCR product, digest it with *Xho* I and *Cla* I restriction enzymes and clone it into the *Xho* I and *Cla* I sites in the pC4:HSA vector.

**[0925]** If an alternative leader sequence is desired, the native albumin leader sequence can be replaced with the chimeric albumin leader, i.e., the HSA-kex2 signal peptide, or an alternative leader by standard methods known in the art. (For example, one skilled in the art could routinely PCR amplify an alternate leader and subclone the PCR product into an albumin fusion construct in place of the albumin leader while maintaining the reading frame).

***EXAMPLE 6: General Expression in Mammalian Cell-Lines.***

**[0926]** An albumin fusion construct generated in an expression vector compatible with expression in mammalian cell-lines can be transfected into appropriate cell-lines by calcium phosphate precipitation, lipofectamine, electroporation, or other transfection methods known in the art and/or as described in Sambrook, Fritsch, and Maniatis. 1989. "Molecular Cloning: A Laboratory Manual, 2nd edition" and in Ausubel et al. 2000. Massachusetts General Hospital and Harvard Medical School "Current Protocols in Molecular Biology", volumes 1-4. The transfected cells are then selected for by the presence of a selecting agent determined by the selectable marker in the expression vector.

**[0927]** The pC4 expression vector (ATCC Accession No. 209646) is a derivative of the plasmid pSV2-DHFR (ATCC Accession No. 37146). pC4 contains the strong promoter Long Terminal Repeats "LTR" of the Rous Sarcoma Virus (Cullen et al., March 1985, Molecular and Cellular Biology, 438-447) and a fragment of the CytoMegaloVirus "CMV"-enhancer (Boshart et al., 1985, Cell 41: 521-530). The vector also contains the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary "CHO" cells or other cell-lines lacking an active DHFR gene are used for transfection. Transfection of an albumin fusion construct in pC4 into CHO cells by methods known in the art will allow for the expression of the albumin fusion protein in CHO cells, followed by leader sequence cleavage, and secretion into the supernatant. The albumin fusion protein is then further purified from the supernatant.

**[0928]** The pEE12.1 expression vector is provided by Lonza Biologics, Inc. (Portsmouth, NH) and is a derivative of pEE6 (Stephens and Cockett, 1989, Nucl. Acids Res. 17: 7110). This vector comprises a promoter, enhancer and complete 5'-untranslated region of the Major Immediate Early gene of the human CytoMegaloVirus, "hCMV-MIE" (International Publication # WO89/01036), upstream of a sequence of interest, and a Glutamine Synthetase gene (Murphy et al., 1991, Biochem J. 227: 277-279; Bebbington et al., 1992, Bio/Technology 10:169-175; US patent US 5,122,464) for purposes of selection of transfected cells in selective methionine sulphoximine containing medium. Transfection of albumin fusion constructs made in pEE12.1 into NS0 cells (International Publication # WO86/05807) by methods known in the art will allow for the expression of the albumin fusion protein in NS0 cells, followed by leader sequence cleavage, and secretion into the supernatant. The albumin fusion protein is then further purified from the supernatant using techniques described herein or otherwise known in the art.

**[0929]** Expression of an albumin fusion protein may be analyzed, for example, by SDS-PAGE

and Western blot, reversed phase HPLC analysis, or other methods known in the art.

**[0930]** Stable CHO and NS0 cell-lines transfected with albumin fusion constructs are generated by methods known in the art (e.g., lipofectamine transfection) and selected, for example, with 100 nM methotrexate for vectors having the DiHydroFolate Reductase 'DHFR' gene as a selectable marker or through growth in the absence of glutamine. Expression levels can be examined for example, by immunoblotting, primarily, with an anti-HSA serum as the primary antibody, or, secondarily, with serum containing antibodies directed to the Therapeutic protein portion of a given albumin fusion protein as the primary antibody.

**[0931]** Expression levels are examined by immunoblot detection with anti-HSA serum as the primary antibody. The specific productivity rates are determined via ELISA in which the capture antibody can be a monoclonal antibody towards the therapeutic protein portion of the albumin fusion and the detecting antibody can be the monoclonal anti-HSA-biotinylated antibody *(or vice versa),* followed by horseradish peroxidase/streptavidin binding and analysis according to the manufacturer's protocol.

***EXAMPLE 7: Expression of an Albumin Fusion Protein in Mammalian Cells.***

**[0932]** The albumin fusion proteins of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

**[0933]** Suitable expression vectors for use in practicing the present invention include, for example, vectors such as, pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, but are not limited to, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

**[0934]** Alternatively, the albumin fusion protein can be expressed in stable cell lines containing the polynucleotide encoding the albumin fusion protein integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, or hygromycin allows the

identification and isolation of the transfected cells.

**[0935]** The transfected polynucleotide encoding the fusion protein can also be amplified to express large amounts of the encoded fusion protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin et al., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page et al., Biotechnology 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

**[0936]** Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

**[0937]** Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

**[0938]** A polynucleotide encoding an albumin fusion protein of the present invention is generated using techniques known in the art and this polynucleotide is amplified using PCR technology known in the art. If a naturally occurring signal sequence is used to produce the fusion protein of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

**[0939]** The amplified fragment encoding the fusion protein of the invention is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

**[0940]** The amplified fragment encoding the albumin fusion protein of the invention is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

**[0941]** Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired fusion protein is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

***EXAMPLE 8: General Purification of an Albumin Fusion Protein Expressed from an Albumin Fusion Construct in Mammalian Cell-lines.***

**[0942]** In preferred embodiments, albumin fusion proteins of the invention comprise the mature form of HSA fused to either the N- or C- terminus of the mature form of a therapeutic protein or portions thereof (e.g., the mature form of a therapeutic protein listed in Table 1, or the mature form of a therapeutic protein shown in Table 2 as SEQ ID NO:Z). In one embodiment of the invention, albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature albumin fusion protein is secreted directly into the culture medium. Albumin fusion proteins of the invention preferably comprise heterologous signal sequences (e.g., the non-native signal sequence of a particular therapeutic protein) including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other

heterologous signal sequences known in the art. Especially preferred as those signal sequence listed in Table 2 and/or the signal sequence listed in the "Expression of Fusion Proteins" and/or "Additional Methods of Recombinant and Synthetic Production of Albumin Fusion Proteins" section of the specification, above. In preferred embodiments, the fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

**[0943]** Albumin fusion proteins from mammalian cell-line supernatants are purified according to different protocols depending on the expression system used.

*Purification from CHO and 293T cell-lines.*

**[0944]** Purification of an albumin fusion protein from CHO cell supernatant or from transiently transfected 293T cell supernatant may involve initial capture with an anionic HQ resin using a sodium phosphate buffer and a phosphate gradient elution, followed by affinity chromatography on a Blue Sepharose FF column using a salt gradient elution. Blue Sepharose FF removes the main BSA/fetuin contaminants. Further purification over the Poros PI 50 resin with a phosphate gradient may remove and lower endotoxin contamination as well as concentrate the albumin fusion protein.

*Purification from NS0 cell-line.*

**[0945]** Purification of an albumin-fusion protein from NS0 cell supernatant may involve Q-Sepharose anion exchange chromatography, followed by SP-sepharose purification with a step elution, followed by Phenyl-650M purification with a step elution, and, ultimately, diafiltration.

**[0946]** The purified protein may then be formulated by buffer exchange.

***EXAMPLE 9: Bacterial Expression of an Albumin Fusion Protein.***

**[0947]** A polynucleotide encoding an albumin fusion protein of the present invention comprising a bacterial signal sequence is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, to synthesize insertion fragments. The primers used to amplify the polynucleotide encoding insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance ($Amp^r$), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

**[0948]** The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated

into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance ($Kan^r$). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

**[0949]** Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D._{600}$) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

**[0950]** Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl or preferably in 8 M urea and concentrations greater than 0.14 M 2-mercaptoethanol by stirring for 3-4 hours at 4°C (see, e.g., Burton et al., Eur. J. Biochem. *179*:379-387 (1989)). The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

**[0951]** Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8. The column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

**[0952]** The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. Exemplary conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

**[0953]** In addition to the above expression vector, the present invention further includes an expression vector, called pHE4a (ATCC Accession Number 209645, deposited on February 25, 1998) which contains phage operator and promoter elements operatively linked to a polynucleotide encoding an albumin fusion protein of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter and operator sequences are made synthetically.

**[0954]** DNA can be inserted into the pHE4a by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to PCR protocols described herein or otherwise known in the art, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

**[0955]** The engineered vector may be substituted in the above protocol to express protein in a bacterial system.

***EXAMPLE 10: Isolation of a Selected cDNA Clone From the Deposited Sample.***

**[0956]** Many of the albumin fusion constructs of the invention have been deposited with the ATCC as shown in Table 3. The albumin fusion constructs may comprise any one of the following expression vectors: the yeast *S. cerevisiae* expression vector pSAC35, the mammalian expression vector pC4, or the mammalian expression vector pEE12.1.

**[0957]** pSAC35 (Sleep *et al.*, 1990, Biotechnology 8:42), pC4 (ATCC Accession No. 209646; Cullen *et al.*, Molecular and Cellular Biology, 438-447 (1985); Boshart *et al.*, Cell 41: 521-530 (1985)), and pEE12.1 (Lonza Biologics, Inc.; Stephens and Cockett, Nucl. Acids Res. 17: 7110 (1989); International Publication #WO89/01036; Murphy *et al.*, Biochem J. 227: 277-279 (1991); Bebbington *et al.*, Bio/Technology 10:169-175 (1992); US patent US 5,122,464; International Publication #WO86/05807) vectors comprise an ampicillin resistance gene for growth in bacterial cells. These vectors and/or an albumin fusion construct comprising them can be transformed into an *E. coli* strain such as Stratagene XL-1 Blue (Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037) using techniques described in the art such as Hanahan, spread onto Luria-Broth agar plates containing 100 μg/mL ampicillin, and grown overnight at 37

°C.

**[0958]** The deposited material in the sample assigned the ATCC Deposit Number cited in Table 3 for any given albumin fusion construct also may contain one or more additional albumin fusion constructs, each encoding different albumin fusion proteins. Thus, deposits sharing the same ATCC Deposit Number contain at least an albumin fusion construct identified in the corresponding row of Table 3.

**[0959]** Two approaches can be used to isolate a particular albumin fusion construct from the deposited sample of plasmid DNAs cited for that albumin fusion construct in Table 3.

*Method 1: Screening*

**[0960]** First, an albumin fusion construct may be directly isolated by screening the sample of deposited plasmid DNAs using a polynucleotide probe corresponding to SEQ ID NO:X for an individual construct ID number in Table 1, using methods known in the art. For example, a specific polynucleotide with 30-40 nucleotides may be synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide can be labeled, for instance, with $^{32}$P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982)). The albumin fusion construct from a given ATCC deposit is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

*Method 2: PCR*

**[0961]** Alternatively, DNA encoding a given albumin fusion protein may be amplified from a sample of a deposited albumin fusion construct with SEQ ID NO:X, for example, by using two primers of 17-20 nucleotides that hybridize to the deposited albumin fusion construct 5' and 3' to the DNA encoding a given albumin fusion protein. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase.

Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

**[0962]** Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)).

**[0963]** Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

**[0964]** This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

**[0965]** This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

***EXAMPLE 11: Multifusion Fusions.***

**[0966]** The albumin fusion proteins (e.g,. containing a Therapeutic protein (or fragment or variant thereof) fused to albumin (or a fragment or variant thereof)) may additionally be fused to other proteins to generate "multifusion proteins". These multifusion proteins can be used for a

variety of applications. For example, fusion of the albumin fusion proteins of the invention to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See e.g,. EP A 394,827; Traunecker et al., Nature 331:84-86 (1988)). Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of an albumin fusion protein. Furthermore, the fusion of additional protein sequences to the albumin fusion proteins of the invention may further increase the solubility and/or stability of the fusion protein. The fusion proteins described above can be made using or routinely modifting techniques known in the art and/or by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule.

**[0967]** Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian or yeast expression vector.

**[0968]** For example, if pC4 (ATCC Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide encoding an albumin fusion protein of the present invention (generateed and isolated using techniques known in the art), is ligated into this BamHI site. Note that the polynucleotide encoding the fusion protein of the invention is cloned without a stop codon, otherwise a Fc containing fusion protein will not be produced.

**[0969]** If the naturally occurring signal sequence is used to produce the albumin fusion protein of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., International Publication No. WO 96/34891.)

**[0970]** Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAGCAC
CTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC
TCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGCCACGAAG
ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG
ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCAC
CGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
AAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA

GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGT
CAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGA
GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG
ACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGG
GGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA
AGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT
(SEQ ID NO:52)

***EXAMPLE 12: Production of an Antibody from an Albumin Fusion Protein.***

*Hybridoma Technology*

**[0971]** Antibodies that bind the albumin fusion proteins of the present invention and portions of the albumin fusion proteins of the present invention (e.g., the Therapeutic protein portion or albumin portion of the fusion protein) can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, a preparation of an albumin fusion protein of the invention or a portion of an albumin fusion protein of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

**[0972]** Monoclonal antibodies specific for an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, are prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention.

**[0973]** Alternatively, additional antibodies capable of binding to an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that

antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the an albumin fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibody can be blocked by the fusion protein of the invention, or a portion of an albumin fusion protein of the invention. Such antibodies comprise anti-idiotypic antibodies to the fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibody and are used to immunize an animal to induce formation of further fusion protein of the invention (or portion of an albumin fusion protein of the invention) -specific antibodies.

**[0974]** For *in vivo* use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., International Publication No. WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985)).

**[0975]** *Isolation Of Antibody Fragments Directed Against an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention From A Library Of scFvs.* Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

**[0976]** *Rescue of the Library.* A library of scFvs is constructed from the RNA of human PBLs as described in International Publication No. WO 92/01047. To rescue phage displaying antibody fragments, approximately $10^9$ *E. coli* harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see International Publication No. WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and

the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in International Publication No. WO 92/01047.

**[0977]** M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately $10^{13}$ transducing units/ml (ampicillin-resistant clones).

**[0978]** *Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately $10^{13}$ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

**[0979]** *Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of

an albumin fusion protein of the invention, or a portion of an albumin fusion protein of the invention, in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., International Publication No. WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

***EXAMPLE 13: [$^3$H]-2-Deoxyglucose Uptake Assay.***

**[0980]** Adipose, skeletal muscle, and liver are insulin-sensitive tissues. Insulin can stimulate glucose uptake/transport into these tissues. In the case of adipose and skeletal muscle, insulin initiates the signal transduction that eventually leads to the translocation of the glucose transporter 4 molecule, GLUT4, from a specialized intracellular compartment to the cell surface. Once on the cell surface, GLUT4 allows for glucose uptake/transport.

*[$^3$H]-2-Deoxyglucose Uptake*

**[0981]** A number of adipose and muscle related cell-lines can be used to test for glucose uptake/transport activity in the absence or presence of a combination of any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. In particular, the 3T3-L1 murine fibroblast cells and the L6 murine skeletal muscle cells can be differentiated into 3T3-L1 adipocytes and into myotubes, respectively, to serve as appropriate *in vitro* models for the [$^3$H]-2-deoxyglucose uptake assay (Urso et al., J Biol Chem, 274(43): 30864-73 (1999); Wang et al., J Mol Endocrinol, 19(3): 241-8 (1997); Haspel et al., J Membr Biol, 169 (1): 45-53 (1999); Tsakiridis et al., Endocrinology, 136(10): 4315-22 (1995)). Briefly, 2 x $10^5$ cells/100 µL of adipocytes or differentiated L6 cells are transferred to 96-well Tissue-Culture, "TC", treated, i.e., coated with 50 µg/mL of poly-L-lysine, plates in post-differentiation medium and are incubated overnight at 37 °C in 5% $CO_2$. The cells are first washed once with serum free low glucose DMEM medium and are then starved with 100 µL/well of the same medium and with 100 µL/well of either buffer or of a combination of any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus, for example, increasing concentrations of 1 nM, 10 nM, and 100 nM of the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) for 16 hours at 37 °C in the absence or presence of 1 nM insulin. The plates are washed three times with 100 µL/well of HEPES buffered saline. Insulin is added at 1 nM in HEPES buffered saline for 30 min at 37 °C in the presence of 10 µM labeled [$^3$H]-2-deoxyglucose (Amersham, #TRK672) and 10 µM unlabeled 2-deoxyglucose

(SIGMA, D-3179). As control, the same conditions are carried out except in the absence of insulin. A final concentration of 10 μM cytochalasin B (SIGMA, C6762) is added at 100 μL/well in a separate well to measure the non-specific uptake. The cells are washed three times with HEPES buffered saline. Labeled, i.e., 10 μM of [$^3$H]-2-deoxyglucose, and unlabeled, i.e., 10 μM of 2-deoxyglucose, are added for 10 minutes at room temperature. The cells are washed three times with cold Phosphate Buffered *Sal* ine, "PBS". The cells are lysed upon the addition of 150 μL/well of 0.2 N NaOH and subsequent incubation with shaking for 20 minutes at room temperature. Samples are then transferred to a scintillation vial to which is added 5 mL of scintillation fluid. The vials are counted in a Beta-Scintillation counter. Uptake in duplicate conditions, the difference being the absence or presence of insulin, is determined with the following equation: [(Insulin counts per minute "cpm" – Non-Specific cpm)/(No Insulin cpm – Non-Specific cpm)]. Average responses fall within the limits of about 5-fold and 3-fold that of controls for adipocytes and myotubes, respectively.

*Differentiation of Cells*

**[0982]** The cells are allowed to become fully confluent in a T-75 cm$^2$ flask. The medium is removed and replaced with 25 mL of pre-differentiation medium for 48 hours. The cells are incubated at 37 °C, in 5% $CO_2$, 85% humidity. After 48 hours, the pre-differentiation medium is removed and replaced with 25 mL differentiation medium for 48 hours. The cells are again incubated at 37 °C, in 5% $CO_2$, 85% humidity. After 48 hours, the medium is removed and replaced with 30 mL post-differentiation medium. Post-differentiation medium is maintained for 14-20 days or until complete differentiation is achieved. The medium is changed every 2-3 days. Human adipocytes can be purchased from Zen-Bio, INC (# SA-1096).

***EXAMPLE 14: In vitro Assay of [$^3$H]-Thymidine Incorporation into Pancreatic Cell-lines.***

**[0983]** It has recently been shown that GLP-1 induces differentiation of the rat pancreatic ductal epithelial cell-line ARIP in a time- and dose-dependent manner which is associated with an increase in Islet Duodenal Homeobox-1 (IDX-1) and insulin mRNA levels (Hui et al., 2001, Diabetes, 50(4): 785-96). The IDX-1 in turn increases mRNA levels of the GLP-1 receptor.

*Cells Types Tested*

**[0984]** RIN-M cells: These cells are available from the American Type Tissue Culture Collection (ATCC Cell Line Number CRL-2057 ). The RIN-M cell line was derived from a radiation induced transplantable rat islet cell tumor. The line was established from a nude mouse xenograft of the tumor. The cells produce and secrete islet polypeptide hormones, and produce L-dopa

decarboxylase (a marker for cells having amine precursor uptake and decarboxylation, or APUD, activity).

**[0985]** ARIP cells: These are pancreatic exocrine cells of epithelial morphology available from the American Type Tissue Culture Collection (ATCC Cell Line Number CRL-1674). See also, references: Jessop, N.W. and Hay, R.J., "Characteristics of two rat pancreatic exocrine cell lines derived from transplantable tumors," In Vitro 16: 212, (1980); Cockell, M. et al., "Identification of a cell-specific DNA-binding activity that interacts with a transcriptional activator of genes expressed in the acinar pancreas," Mol. Cell. Biol. 9: 2464-2476, (1989); Roux, E., et al. "The cell-specific transcription factor PTF1 contains two different subunits that interact with the DNA" Genes Dev. 3: 1613-1624, (1989); and, Hui, H., et al., "Glucagon-like peptide 1 induces differentiation of islet duodenal homeobox-1-positive pancreatic ductal cells into insulin-secreting cells," Diabetes 50: 785-796 (2001).

*Preparation of Cells*

**[0986]** The RIN-M cell-line is grown in RPMI 1640 medium (Hyclone, #SH300027.01) with 10% fetal bovine serum (HyClone, #SH30088.03) and is subcultured every 6 to 8 days at a ratio of 1:3 to 1:6. The medium is changed every 3 to 4 days.

**[0987]** The ARIP (ATCC #CRL-1674) cell-line is grown in Ham's F12K medium (ATCC, #30-2004) with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate and 10% fetal bovine serum. The ARIP cell-line is subcultured at a ratio of 1:3 to 1:6 twice per week. The medium is changed every 3 to 4 days.

*Assay Protocol*

**[0988]** The cells are seeded at 4000 cells/well in 96-well plates and cultured for 48 to 72 hours to 50% confluence. The cells are switched to serum-free media at 100 μL/well. After incubation for 48-72 hours, serum and/or the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof) are added to the well. Incubation persists for an additional 36 hours. [$^3$H]-Thymidine (5-20 Ci/mmol) (Amersham Pharmacia, #TRK120) is diluted to 1 microCuries/5 microliters. After the 36 hour incubation, 5 microliters is added per well for a further 24 hours. The reaction is terminated by washing the cells gently with cold Phosphate-Buffered *Sal* ine, "PBS", once. The cells are then fixed with 100 microliters of 10% ice cold TCA for 15 min at 4 °C. The PBS is removed and 200 microliters of 0.2 N NaOH is added. The plates are incubated for 1 hour at room temperature with shaking. The solution is transferred to a scintillation vial and 5 mL of scintillation fluid compatible with aqueous solutions is added and mixed vigorously. The vials are counted in a beta scintillation

counter. As negative control, only buffer is used. As a positive control fetal calf serum is used.

***EXAMPLE 15: Assaying for Glycosuria.***

**[0989]** Glycosuria (i.e., excess sugar in the urine), can be readily assayed to provide an index of the disease state of diabetes mellitus. Excess urine in a patient sample as compared with a normal patient sample is symptomatic of IDDM and NIDDM. Efficacy of treatment of such a patient having IDDM and NIDDM is indicated by a resulting decrease in the amount of excess glucose in the urine. In a preferred embodiment for IDDM and NIDDM monitoring, urine samples from patients are assayed for the presence of glucose using techniques known in the art. Glycosuria in humans is defined by a urinary glucose concentration exceeding 100 mg per 100 ml. Excess sugar levels in those patients exhibiting glycosuria can be measured even more precisely by obtaining blood samples and assaying serum glucose.

***EXAMPLE 16: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation.***

**[0990]** Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

**[0991]** One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

**[0992]** In Vitro Assay- Albumin fusion proteins of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin) can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of an albumin

fusion protein of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220) .

**[0993]** Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added $10^5$ B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X $10^{-5}$M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and $10^{-5}$ dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

**[0994]** *In vivo* Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of an albumin fusion protein of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin). Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with the albumin fusion protein of the invention identify the results of the activity of the fusion protein on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

**[0995]** Flow cytometric analyses of the spleens from mice treated with the albumin fusion protein is used to indicate whether the albumin fusion protein specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

**[0996]** Likewise, a predicted consequence of increased mature B-cell representation *in vivo* is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared

between buffer and fusion protein treated mice.

***EXAMPLE 17: T Cell Proliferation Assay.***

**[0997]** A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of $^{3}$H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x $10^{4}$/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of an albumin fusion protein of the invention (including fusion proteins containing fragments or variants of Therapeutic proteins and/or albumin or fragments or variants of albumin) (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 µl of supernatant is removed and stored –20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of medium containing 0.5 uCi of $^{3}$H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of $^{3}$H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative control for the effects of fusion proteins of the invention.

***EXAMPLE 18: Effect of Fusion Proteins of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells.***

**[0998]** Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

**[0999]** FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of an albumin fusion protein of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated

with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

**[1000]** Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Thl helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ($10^6$/ml) are treated with increasing concentrations of an albumin fusion protein of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

**[1001]** Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increased expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

**[1002]** FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of an albumin fusion protein of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

**[1003]** Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Albumin fusion proteins of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

**[1004]** Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated processes (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the fusion protein to be tested. Cells are suspended at a concentration of 2 x $10^6$/ml in PBS containing PI at a final concentration of 5 μg/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

**[1005]** Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of $5x10^5$ cells/ml with increasing concentrations of an albumin fusion protein of the invention and under the same conditions, but in the absence of the fusion protein. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in the presence of the fusion protein. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

**[1006]** Oxidative burst. Purified monocytes are plated in 96-w plate at $2\text{-}1x10^5$ cell/well. Increasing concentrations of an albumin fusion protein of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 μl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of $H_2O_2$ produced by the macrophages, a standard curve of a $H_2O_2$ solution of known molarity is performed for each experiment.

***EXAMPLE 19: The Effect of Albumin Fusion Proteins of the Invention on the Growth of Vascular Endothelial Cells.***

**[1007]** On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2-5x$10^4$ cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An albumin fusion protein of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

**[1008]** An increase in the number of HUVEC cells indicates that the fusion protein may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cells indicates that the fusion protein inhibits vascular endothelial cells.

***EXAMPLE 20: Rat Corneal Wound Healing Model.***

**[1009]** This animal model shows the effect of an albumin fusion protein of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

Inserting a spatula below the lip of the incision facing the outer corner of the eye.

Making a pocket (its base is 1-1.5 mm form the edge of the eye).

Positioning a pellet, containing 50ng- 5ug of an albumin fusion protein of the invention, within the pocket.

Treatment with an an albumin fusion protein of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

***EXAMPLE 21: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models.***

*Diabetic db+/db+ Mouse Model.*

**[1010]** To demonstrate that an albumin fusion protein of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al., J. Surg. Res. 52*:389 (1992); Greenhalgh, D.G. *et al., Am. J. Pathol. 136*:1235 (1990)).

**[1011]** The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA 77*:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+)

have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol. 120*:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol. 51(1)*:1-7 (1983); Leiter *et al.*, *Am. J. of Pathol. 114*:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol. 83(2)*:221-232 (1984); Robertson *et al.*, *Diabetes 29(1)*:60-67 (1980); Giacomelli *et al.*, *Lab Invest. 40(4)*:460-473 (1979); Coleman, D.L., *Diabetes 31 (Suppl)*:1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol. 120*:1375-1377 (1978)).

**[1012]** The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol. 136*:1235-1246 (1990)).

**[1013]** Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

**[1014]** Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med. 172*:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

**[1015]** Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is

covered by a continuous epithelium.

**[1016]** An albumin fusion protein of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

**[1017]** Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

**[1018]** Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

**[1019]** Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

a. [Open area on day 8] - [Open area on day 1] / [Open area on day 1]

**[1020]** Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an albumin fusion protein of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al., Am. J. Pathol. 136:*1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

**[1021]** Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

**[1022]** Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control.

Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

**[1023]** Experimental data are analyzed using an unpaired t test. A p value of $< 0.05$ is considered significant.

*Steroid Impaired Rat Model*

**[1024]** The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl*et al., J. Immunol. 115*: 476-481 (1975); Werb *et al., J. Exp. Med. 147*:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al., An. Intern. Med. 37*:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In:* Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In*: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al., Proc. Natl. Acad. Sci. USA 86*: 2229-2233 (1989)).

**[1025]** To demonstrate that an albumin fusion protein of the invention can accelerate the healing process, the effects of multiple topical applications of the fusion protein on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

**[1026]** Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the

Care and Use of Laboratory Animals.

**[1027]** The wounding protocol is followed according to that described above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

**[1028]** Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

**[1029]** The fusion protein of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

**[1030]** Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

**[1031]** Three groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

**[1032]** Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

b. [Open area on day 8] - [Open area on day 1] / [Open area on day 1]

**[1033]** Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds.

Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an albumin fusion protein of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

**[1034]** Experimental data are analyzed using an unpaired t test. A p value of $< 0.05$ is considered significant.

***EXAMPLE 22: Lymphedema Animal Model.***

**[1035]** The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an albumin fusion protein of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

**[1036]** Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

**[1037]** Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

**[1038]** Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

**[1039]** Care is taken to control any mild bleeding resulting from this procedure. After lymphatics

are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

**[1040]** To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect of plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

**[1041]** Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people and those 2 readings are averaged. Readings are taken from both control and edematous limbs.

**[1042]** Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), and both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

**[1043]** Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and $Ca2^{+}$ comparison.

**[1044]** Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

**[1045]** Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

***EXAMPLE 23: Suppression of TNF alpha-Induced Adhesion Molecule Expression by an Albumin Fusion Protein of the Invention.***

**[1046]** The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

**[1047]** Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

**[1048]** The potential of an albumin fusion protein of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

**[1049]** To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% $CO_2$. HUVECs are seeded in 96-well plates at concentrations of 1 x $10^4$ cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

**[1050]** Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with $Ca^{++}$ and $Mg^{++}$) is added to each well. Plates are held at 4°C for 30 min.

**[1051]** Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 µl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

**[1052]** Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 ($10^0$) > $10^{-0.5}$ > $10^{-1}$ > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

***EXAMPLE 24: Construction of GAS Reporter Construct.***

**[1053]** One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

**[1054]** GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

**[1055]** The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine

phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

**[1056]** The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995)). A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:53)).

**[1057]** Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway. Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway (See Table 5, below). Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

**Table 5**

| | JAKs | | | | STATS | GAS(elements) or ISRE |
|---|---|---|---|---|---|---|
| Ligand | tyk2 | Jak1 | Jak2 | Jak3 | | |
| IFN family | | | | | | |
| IFN-a/B | + | + | - | - | 1,2,3 | ISRE |
| IFN-g | | + | + | - | 1 | GAS (IRF1>Lys6>IFP) |
| Il-10 | + | ? | ? | - | 1,3 | |
| gp130 family | | | | | | |
| IL-6 (Pleiotropic) | + | + | + | ? | 1,3 | GAS(IRF1>Lys6>IFP) |
| Il-11(Pleiotropic) | ? | + | ? | ? | 1,3 | |
| OnM(Pleiotropic) | ? | + | + | ? | 1,3 | |
| LIF(Pleiotropic) | ? | + | + | ? | 1,3 | |
| CNTF(Pleiotropic) | -/+ | + | + | ? | 1,3 | |
| G-CSF(Pleiotropic) | ? | + | ? | ? | 1,3 | |
| IL-12(Pleiotropic) | + | - | + | + | 1,3 | |
| g-C family | | | | | | |
| IL-2 (lymphocytes) | - | + | - | + | 1,3,5 | GAS |
| IL-4 (lymph/myeloid) | - | + | - | + | 6 | GAS(IRF1=IFP>>Ly6)(IgH) |

| | | | | | | |
|---|---|---|---|---|---|---|
| IL-7 (lymphocytes) | - | + | - | + | 5 | GAS |
| IL-9 (lymphocytes) | - | + | - | + | 5 | GAS |
| IL-13 (lymphocyte) | - | + | ? | ? | 6 | GAS |
| IL-15 | ? | + | ? | + | 5 | GAS |
| gp140 family | | | | | | |
| IL-3 (myeloid) | - | - | + | - | 5 | GAS(IRF1>IFP>>Ly6) |
| IL-5 (myeloid) | - | - | + | - | 5 | GAS |
| GM-CSF (myeloid) | - | - | + | - | 5 | GAS |
| Growth hormone family | | | | | | |
| GH | ? | - | + | - | 5 | |
| PRL | ? | +/- | + | - | 1,3,5 | |
| EPO | ? | - | + | - | 5 | GAS (B-CAS>IRF1=IFP>>Ly6) |
| Receptor Tyrosine Kinases | | | | | | |
| EGF | ? | + | + | - | 1,3 | GAS (IRF1) |
| PDGF | ? | + | + | - | 1,3 | |
| CSF-1 | ? | + | + | - | 1,3 | GAS(not IRF1) |

**[1058]** To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 27-29, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGA TTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:54)

**[1059]** The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:55)

**[1060]** PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGATTTC CCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGC CCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAAT

TTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAG TGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:56)

**[1061]** With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

**[1062]** The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

**[1063]** Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 27-29.

**[1064]** Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing EGR and NF-KB promoter sequences are described in Examples 27-31. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

***EXAMPLE 25: Assay for SEAP Activity.***

**[1065]** As a reporter molecule for the assays described in examples disclosed herein, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

**[1066]** Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer

into Optiplates containing 35 ul of a solution containing an albumin fusion protein of the invention. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

**[1067]** Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the Table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on a luminometer, thus one should treat 5 plates at each time and start the second set 10 minutes later.

**[1068]** Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

**Table 6**

| # of plates | Rxn buffer diluent (ml) | CSPD (ml) | # of plates | Rxn buffer diluent (ml) | CSPD (ml) |
|---|---|---|---|---|---|
| 10 | 60 | 3 | 31 | 165 | 8.25 |
| 11 | 65 | 3.25 | 32 | 170 | 8.5 |
| 12 | 70 | 3.5 | 33 | 175 | 8.75 |
| 13 | 75 | 3.75 | 34 | 180 | 9 |
| 14 | 80 | 4 | 35 | 185 | 9.25 |
| 15 | 85 | 4.25 | 36 | 190 | 9.5 |
| 16 | 90 | 4.5 | 37 | 195 | 9.75 |
| 17 | 95 | 4.75 | 38 | 200 | 10 |
| 18 | 100 | 5 | 39 | 205 | 10.25 |
| 19 | 105 | 5.25 | 40 | 210 | 10.5 |
| 20 | 110 | 5.5 | 41 | 215 | 10.75 |
| 21 | 115 | 5.75 | 42 | 220 | 11 |
| 22 | 120 | 6 | 43 | 225 | 11.25 |
| 23 | 125 | 6.25 | 44 | 230 | 11.5 |
| 24 | 130 | 6.5 | 45 | 235 | 11.75 |
| 25 | 135 | 6.75 | 46 | 240 | 12 |
| 26 | 140 | 7 | 47 | 245 | 12.25 |
| 27 | 145 | 7.25 | 48 | 250 | 12.5 |
| 28 | 150 | 7.5 | 49 | 255 | 12.75 |
| 29 | 155 | 7.75 | 50 | 260 | 13 |
| 30 | 160 | 8 | | | |

***EXAMPLE 26: Assay Identifying Neuronal Activity.***

**[1069]** When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of

EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, the ability of fusion proteins of the invention to activate cells can be assessed.

**[1070]** Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by an albumin fusion protein of the present invention can be assessed.

**[1071]** The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

First primer: 5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG-3' (SEQ ID NO:57)

Second primer: 5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:58)

**[1072]** Using the GAS:SEAP/Neo vector produced in Example 24, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

**[1073]** To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

**[1074]** PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

**[1075]** Transfect the EGR/SEAP/Neo construct into PC12 using techniques known in the art. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

**[1076]** To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is

screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

**[1077]** The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

**[1078]** Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add a series of different concentrations of an albumin fusion protein of the inventon, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay may be routinely performed using techniques known in the art and/or as described in Example 25.

***EXAMPLE 27: Assay for T-cell Activity.***

**[1079]** The following protocol is used to assess T-cell activity by identifying factors, and determining whether an albumin fusion protein of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 24. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

**[1080]** Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

**[1081]** Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

**[1082]** During the incubation period, count cell concentration, spin down the required number of cells ($10^7$ per transfection), and resuspend in OPTI-MEM to a final concentration of $10^7$ cells/ml. Then add 1ml of 1 x $10^7$ cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

**[1083]** The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with varying concentrations of one or more fusion proteins of the present invention.

**[1084]** On the day of treatment with the fusion protein, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of fusion proteins and the number of different concentrations of fusion proteins being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

**[1085]** The well dishes containing Jurkat cells treated with the fusion protein are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 25. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

**[1086]** As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

**[1087]** The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

***EXAMPLE 28: Assay for T-cell Activity.***

**[1088]** NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

**[1089]** In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by

NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

**[1090]** Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the fusion protein. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

**[1091]** To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:59), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCAT CCTGCCATCTCAATTAG:3' (SEQ ID NO:60)

**[1092]** The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:55)

**[1093]** PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATCTGCC ATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAA CTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCA GAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTT GGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:61)

**[1094]** Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

**[1095]** In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

**[1096]** Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 25. Similarly, the method for assaying fusion proteins with these stable Jurkat T-cells is also described in Example 25. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

***EXAMPLE 29: Assay Identifying Myeloid Activity.***

**[1097]** The following protocol is used to assess myeloid activity of an albumin fusion protein of the present invention by determining whether the fusion protein proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 24. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

**[1098]** To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 24, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

**[1099]** Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37 degrees C for 45 min.

**[1100]** Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

**[1101]** The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

**[1102]** These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

**[1103]** Add different concentrations of the fusion protein. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to methods known in the art and/or the protocol described in

Example 25.

***EXAMPLE 30: Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability.***

**[1104]** Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify fusion proteins which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

**[1105]** The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

**[1106]** For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a $CO_2$ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

**[1107]** A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a $CO_2$ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

**[1108]** For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x$10^6$ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x$10^6$ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

**[1109]** For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The fusion protein of the invention is added to the well, and a change in fluorescence is detected.

**[1110]** To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul.

Increased emission at 530 nm indicates an extracellular signaling event caused by an albumin fusion protein of the present invention or a molecule induced by an albumin fusion protein of the present invention, which has resulted in an increase in the intracellular $Ca^{++}$ concentration.

***EXAMPLE 31: Assay Identifying Tyrosine Kinase Activity.***

**[1111]** The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

**[1112]** Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

**[1113]** Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether an albumin fusion protein of the present invention or a molecule induced by a fusion proetin of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

**[1114]** Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

**[1115]** To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or a different concentrations of an albumin fusion protein of the invention, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN)) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

**[1116]** Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

**[1117]** Generally, the tyrosine kinase activity of an albumin fusion protein of the invention is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

**[1118]** The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/$Mg_{2+}$ (5mM ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

**[1119]** The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

**[1120]** Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP

module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

**[1121]** Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

***EXAMPLE 32: Assay Identifying Phosphorylation Activity.***

**[1122]** As a potential alternative and/or complement to the assay of protein tyrosine kinase activity described in Example 31, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

**[1123]** Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

**[1124]** A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or varying concentrations of the fusion protein of the invention for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

**[1125]** After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing

reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by the fusion protein of the present invention or a molecule induced by an albumin fusion protein of the present invention.

***EXAMPLE 33: Phosphorylation Assay.***

**[1126]** In order to assay for phosphorylation activity of an albumin fusion protein of the invention, a phosphorylation assay as described in U.S. Patent 5,958,405 (which is herein incorporated by reference) is utilized. Briefly, phosphorylation activity may be measured by phosphorylation of a protein substrate using gamma-labeled $^{32}$P-ATP and quantitation of the incorporated radioactivity using a gamma radioisotope counter. The fusion portein of the invention is incubated with the protein substrate, $^{32}$P-ATP, and a kinase buffer. The $^{32}$P incorporated into the substrate is then separated from free $^{32}$P-ATP by electrophoresis, and the incorporated $^{32}$P is counted and compared to a negative control. Radioactivity counts above the negative control are indicative of phosphorylation activity of the fusion protein.

***EXAMPLE 34: Detection of Phosphorylation Activity (Activation) of an Albumin Fusion Protein of the Invention in the Presence of Polypeptide Ligands.***

**[1127]** Methods known in the art or described herein may be used to determine the phosphorylation activity of an albumin fusion protein of the invention. A preferred method of determining phosphorylation activity is by the use of the tyrosine phosphorylation assay as described in US 5,817,471 (incorporated herein by reference).

***EXAMPLE 35: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation.***

**[1128]** This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of fusion proteins of the inventon to stimulate proliferation of CD34+ cells.

**[1129]** It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of fusion proteins of the invention on hematopoietic activity of a wide range of progenitor cells, the assay contains a given fusion protein of the invention in the presence or absence of hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested fusion protein has a stimulatory effect on hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a

low level of cycling cells, it is likely that any inhibitory effect of a given fusion protein might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

**[1130]** Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5 x $10^5$ cells/ml. During this time, 100 µl of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with an albumin fusion protein of the invention in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 µl of prepared cytokines, varying concentrations of an albumin fusion protein of the invention, and 20 µl of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 µl. The plates are then placed in a 37°C/5% $CO_2$ incubator for five days.

**[1131]** Eighteen hours before the assay is harvested, 0.5 µCi/well of [3H] Thymidine is added in a 10 µl volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 µl Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates are then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

**[1132]** The studies described in this example test the activity of a given fusion protein to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of fusion porteins and polynucleotides of the invention (e.g., gene therapy) as well as agonists and antagonists thereof. The ability of an albumin fusion protein of the invention to stimulate the proliferation of bone marrow CD34+ cells indicates that the albumin fusion protein and/or polynucleotides corresponding to the fusion protein are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections

above, and elsewhere herein.

***EXAMPLE 36: Assay for Extracellular Matrix Enhanced Cell Response (EMECR).***

**[1133]** The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to evaluate the ability of fusion proteins of the invention to act on hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

**[1134]** Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5.\beta_1$ and $\alpha_4.\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and are responsible for stimulating stem cell self-renewal havea not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

**[1135]** Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of 0.2 μg/ $cm^2$. Mouse bone marrow cells are plated (1,000 cells/well ) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 ( 5 ng/ml ) + SCF ( 50 ng/ml ) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Albumin fusion proteins of the invention are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where volume of the administed composition containing the albumin fusion protein of the invention represents 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment ( 5% $CO_2$, 7% $O_2$, and 88% $N_2$ ) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

**[1136]** If a particular fusion protein of the present invention is found to be a stimulator of hematopoietic progenitors, the fusion protein and polynucleotides corresponding to the fusion protein may be useful for example, in the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity"

and "Infectious Disease" sections above, and elsewhere herein. The fusion protein may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

**[1137]** Additionally, the albumin fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

**[1138]** Moreover, fusion proteins of the invention and polynucleotides encoding albumin fusion proteins of the invention may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

***EXAMPLE 37: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation.***

**[1139]** An albumin fusion protein of the invention is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the fusion protein on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

**[1140]** Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 µl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 µg/ml hEGF, 5mg/ml insulin, 1µg/ml hFGF, 50mg/ml gentamycin, 50 µg/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media

for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37 °C until day 2.

**[1141]** On day 2, serial dilutions and templates of an albumin fusion protein of the invention are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or an albumin fusion protein of the invention and incubate at 37 degrees C/5% $CO_2$ until day 5.

**[1142]** Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4 degrees C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

**[1143]** On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

**[1144]** On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

**[1145]** Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels.

**[1146]** Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

**[1147]** A positive result in this assay suggests AoSMC cell proliferation and that the albumin fusion protein may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of the fusion protein and polynucleotides encoding the albumin fusion protein. For example, inflammation and immune

responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, fusion proteins may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, fusion proteins showing antagonistic activity in this assay may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular agent (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, albumin fusion proteins that act as antagonists in this assay may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

***EXAMPLE 38: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells.***

**[1148]** The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

**[1149]** Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and

replaced with 100 µl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing (containing an albumin fusion protein of the invention) and positive or negative controls are added to the plate in triplicate (in 10 µl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 µl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 µl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 ($10^0$) > $10^{-0.5}$ > $10^{-1}$ > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

***EXAMPLE 39: Alamar Blue Endothelial Cells Proliferation Assay.***

**[1150]** This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a

non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

**[1151]** Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37 degreesC overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of an albumin fusion protein of the invention or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

**[1152]** Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form (i.e., stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity). The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

***EXAMPLE 40: Detection of Inhibition of a Mixed Lymphocyte Reaction.***

**[1153]** This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by fusion proteins of the invention. Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by the albumin fusion proteins that inhibit MLR since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

**[1154]** Albumin fusion proteins of the invention found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis,

inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

**[1155]** Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x $10^6$ cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x $10^5$ cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of the fusion protein test material (50 µl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 µg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 µg/ml. Cells are cultured for 7-8 days at 37°C in 5% $CO_2$, and 1 µC of [$^3$H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

**[1156]** Samples of the fusion protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

***EXAMPLE 41: Assays for Protease Activity.***

**[1157]** The following assay may be used to assess protease activity of an albumin fusion protein of the invention.

**[1158]** Gelatin and casein zymography are performed essentially as described (Heusen et al., *Anal. Biochem.*, 102:196-202 (1980); Wilson et al., *Journal of Urology*, 149:653-658 (1993)). Samples are run on 10% polyacryamide/0.1% SDS gels containing 1% gelain orcasein, soaked in 2.5% triton at room temperature for 1 hour, and in 0.1M glycine, pH 8.3 at 37°C 5 to 16 hours. After staining in amido black areas of proteolysis apear as clear areas agains the blue-black background. Trypsin (Sigma T8642) is used as a positive control.

**[1159]** Protease activity is also determined by monitoring the cleavage of n-a-benzoyl-L-arginine ethyl ester (BAEE) (Sigma B-4500. Reactions are set up in (25mM$NaPO_4$,1mM EDTA, and 1mM BAEE), pH 7.5. Samples are added and the change in adsorbance at 260nm is monitored on the Beckman DU-6 spectrophotometer in the time-drive mode. Trypsin is used as a positive

control.

[1160] Additional assays based upon the release of acid-soluble peptides from casein or hemoglobin measured as adsorbance at 280 nm or colorimetrically using the Folin method are performed as described in Bergmeyer, et al., *Methods of Enzymatic Analysis*, 5 (1984). Other assays involve the solubilization of chromogenic substrates (Ward, *Applied Science*, 251-317 (1983)).

***EXAMPLE 42: Identifying Serine Protease Substrate Specificity.***

[1161] Methods known in the art or described herein may be used to determine the substrate specificity of the albumin fusion proteins of the present invention having serine protease activity. A preferred method of determining substrate specificity is by the use of positional scanning synthetic combinatorial libraries as described in GB 2 324 529 (incorporated herein in its entirety).

***EXAMPLE 43: Ligand Binding Assays.***

[1162] The following assay may be used to assess ligand binding activity of an albumin fusion protein of the invention.

[1163] Ligand binding assays provide a direct method for ascertaining receptor pharmacology and are adaptable to a high throughput format. The purified ligand for an albumin fusion protein of the invention is radiolabeled to high specific activity (50-2000 Ci/mmol) for binding studies. A determination is then made that the process of radiolabeling does not diminish the activity of the ligand towards the fusion protein. Assay conditions for buffers, ions, pH and other modulators such as nucleotides are optimized to establish a workable signal to noise ratio for both membrane and whole cell polypeptide sources. For these assays, specific polypeptide binding is defined as total associated radioactivity minus the radioactivity measured in the presence of an excess of unlabeled competing ligand. Where possible, more than one competing ligand is used to define residual nonspecific binding.

***EXAMPLE 44: Functional Assay in Xenopus Oocytes.***

[1164] Capped RNA transcripts from linearized plasmid templates encoding an albumin fusion protein of the invention is synthesized in vitro with RNA polymerases in accordance with standard procedures. In vitro transcripts are suspended in water at a final concentration of 0.2 mg/mi. Ovarian lobes are removed from adult female toads, Stage V defolliculated oocytes are obtained, and RNA transcripts (10 ng/oocytc) are injected in a 50 nl bolus using a microinjection apparatus. Two electrode voltage clamps are used to measure the currents from individual *Xenopus oocytes* in response fusion protein and polypeptide agonist exposure. Recordings are

made in Ca2+ free Barth's medium at room temperature. The Xenopus system can be used to screen known ligands and tissue/cell extracts for activating ligands.

***EXAMPLE 45: Microphysiometric Assays.***

**[1165]** Activation of a wide variety of secondary messenger systems results in extrusion of small amounts of acid from a cell. The acid formed is largely as a result of the increased metabolic activity required to fuel the intracellular signaling process. The pH changes in the media surrounding the cell are very small but are detectable by the CYTOSENSOR microphysiometer (Molecular Devices Ltd., Menlo Park, Calif.). The CYTOSENSOR is thus capable of detecting the ability of an albumin fusion protein of the invention to activate secondary messengers that are coupled to an energy utilizing intracellular signaling pathway.

***EXAMPLE 46: Extract/Cell Supernatant Screening.***

**[1166]** A large number of mammalian receptors exist for which there remains, as yet, no cognate activating ligand (agonist). Thus, active ligands for these receptors may not be included within the ligands banks as identified to date. Accordingly, the albumin fusion proteins of the invention can also be functionally screened (using calcium, cAMP, microphysiometer, oocyte electrophysiology, etc., functional screens) against tissue extracts to identify natural ligands for the Therapeutic protein portion and/or albumin protein portion of an albumin fusion protein of the invention. Extracts that produce positive functional responses can be sequentially subfractionated until an activating ligand is isolated and identified.

***EXAMPLE 47: ATP-binding assay.***

**[1167]** The following assay may be used to assess ATP-binding activity of fusion proteins of the invention.

**[1168]** ATP-binding activity of an albumin fusion protein of the invention may be detected using the ATP-binding assay described in U.S. Patent 5,858,719, which is herein incorporated by reference in its entirety. Briefly, ATP-binding to an albumin fusion protein of the invention is measured via photoaffinity labeling with 8-azido-ATP in a competition assay. Reaction mixtures containing 1 mg/ml of ABC transport protein are incubated with varying concentrations of ATP, or the non-hydrolyzable ATP analog adenyl-5'-imidodiphosphate for 10 minutes at 4°C. A mixture of 8-azido-ATP (Sigma Chem. Corp., St. Louis, MO.) plus 8-azido-ATP ($^{32}$P-ATP) (5 mCi/μmol, ICN, Irvine CA.) is added to a final concentration of 100 μM and 0.5 ml aliquots are placed in the wells of a porcelain spot plate on ice. The plate is irradiated using a short wave 254 nm UV lamp at a distance of 2.5 cm from the plate for two one-minute intervals with a one-minute cooling interval in between. The reaction is stopped by addition of dithiothreitol to a final

concentration of 2mM. The incubations are subjected to SDS-PAGE electrophoresis, dried, and autoradiographed. Protein bands corresponding to the albumin fusion proteins of the invention are excised, and the radioactivity quantified. A decrease in radioactivity with increasing ATP or adenly-5'-imidodiphosphate provides a measure of ATP affinity to the fusion protein.

***EXAMPLE 48: Identification Of Signal Transduction Proteins That Interact With An albumin fusion protein Of The Present Invention.***

**[1169]** Albumin fusion proteins of the invention may serve as research tools for the identification, characterization and purification of signal transduction pathway proteins or receptor proteins. Briefly, a labeled fusion protein of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, an albumin fusion protein of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as carcinoma tissues, is passed over the column, and molecules with appropriate affinity bind to the albumin fusion protein. The protein complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning the relevant gene from an appropriate cDNA library.

***EXAMPLE 49: IL-6 Bioassay.***

**[1170]** A variety of assays are known in the art for testing the proliferative effects of an albumin fusion protein of the invention. For example, one such asssay is the IL-6 Bioassay as described by Marz *et al.* (*Proc. Natl. Acad. Sci., U.S.A., 95*:3251-56 (1998), which is herein incorporated by reference). After 68 hrs. at 37°C, the number of viable cells is measured by adding the tetrazolium salt thiazolyl blue (MTT) and incubating for a further 4 hrs. at 37°C. B9 cells are lysed by SDS and optical density is measured at 570 nm. Controls containing IL-6 (positive) and no cytokine (negative) are Briefly, IL-6 dependent B9 murine cells are washed three times in IL-6 free medium and plated at a concentration of 5,000 cells per well in 50 µl, and 50 µl of fusion protein of the invention is added. utilized. Enhanced proliferation in the test sample(s) (containing an albumin fusion protein of the invention) relative to the negative control is indicative of proliferative effects mediated by the fusion protein.

***EXAMPLE 50: Support of Chicken Embryo Neuron Survival.***

**[1171]** To test whether sympathetic neuronal cell viability is supported by an albumin fusion protein of the invention, the chicken embryo neuronal survival assay of Senaldi *et al* may be utilized (*Proc. Natl. Acad. Sci., U.S.A., 96*:11458-63 (1998), which is herein incorporated by

reference). Briefly, motor and sympathetic neurons are isolated from chicken embryos, resuspended in L15 medium (with 10% FCS, glucose, sodium selenite, progesterone, conalbumin, putrescine, and insulin; Life Technologies, Rockville, MD.) and Dulbecco's modified Eagles medium [with 10% FCS, glutamine, penicillin, and 25 mM Hepes buffer (pH 7.2); Life Technologies, Rockville, MD.], respectively, and incubated at 37°C in 5% $CO_2$ in the presence of different concentrations of the purified fusion protein of the invention, as well as a negative control lacking any cytokine. After 3 days, neuron survival is determined by evaluation of cellular morphology, and through the use of the colorimetric assay of Mosmann (Mosmann, T., *J. Immunol. Methods, 65*:55-63 (1983)). Enhanced neuronal cell viability as compared to the controls lacking cytokine is indicative of the ability of the albumin fusion protein to enhance the survival of neuronal cells.

***EXAMPLE 51: Assay for Phosphatase Activity.***

**[1172]** The following assay may be used to assess serine/threonine phosphatase (PTPase) activity of an albumin fusion protein of the invention.

**[1173]** In order to assay for serine/threonine phosphatase (PTPase) activity, assays can be utilized which are widely known to those skilled in the art. For example, the serine/threonine phosphatase (PSPase) activity of an albumin fusion protein of the invention may be measured using a PSPase assay kit from New England Biolabs, Inc. Myelin basic protein (MyBP), a substrate for PSPase, is phosphorylated on serine and threonine residues with cAMP-dependent Protein Kinase in the presence of [$^{32}$P]ATP. Protein serine/threonine phosphatase activity is then determined by measuring the release of inorganic phosphate from 32P-labeled MyBP.

***EXAMPLE 52: Interaction of Serine/Threonine Phosphatases with other Proteins.***

**[1174]** Fusion proteins of the invention having serine/threonine phosphatase activity ( e.g., as determined in Example 51) are useful, for example, as research tools for the identification, characterization and purification of additional interacting proteins or receptor proteins, or other signal transduction pathway proteins. Briefly, a labeled fusion protein of the invention is useful as a reagent for the purification of molecules with which it interacts. In one embodiment of affinity purification, an albumin fusion protein of the invention is covalently coupled to a chromatography column. Cell-free extract derived from putative target cells, such as neural or liver cells, is passed over the column, and molecules with appropriate affinity bind to the fusion protein. The fusion protein -complex is recovered from the column, dissociated, and the recovered molecule subjected to N-terminal protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotide probes for cloning

the relevant gene from an appropriate cDNA library.

***EXAMPLE 53: Assaying for Heparanase Activity.***

**[1175]** There a numerous assays known in the art that may be employed to assay for heparanase activity of an albumin fusion protein of the invention. In one example, heparanase activity of an albumin fusion protein of the invention, is assayed as described by Vlodavsky et al., (Vlodavsky et al., Nat. Med., 5:793-802 (1999)). Briefly, cell lysates, conditioned media, intact cells ($1 \times 10^6$ cells per 35-mm dish), cell culture supernatant, or purified fusion protein are incubated for 18 hrs at 37°C, pH 6.2-6.6, with $^{35}S$-labeled ECM or soluble ECM derived peak I proteoglycans. The incubation medium is centrifuged and the supernatant is analyzed by gel filtration on a Sepharose CL-6B column (0.9 x 30 cm). Fractions are eluted with PBS and their radioactivity is measured. Degradation fragments of heparan sulfate side chains are eluted from Sepharose 6B at $0.5 < K_{av} < 0.8$ (peak II). Each experiment is done at least three times. Degradation fragments corresponding to "peak II," as described by Vlodavsky et al., is indicative of the activity of an albumin fusion protein of the invention in cleaving heparan sulfate.

***EXAMPLE 54: Immobilization of biomolecules.***

**[1176]** This example provides a method for the stabilization of an albumin fusion protein of the invention in non-host cell lipid bilayer constucts (see, e.g., Bieri et al., Nature Biotech 17:1105-1108 (1999), hereby incorporated by reference in its entirety herein) which can be adapted for the study of fusion proteins of the invention in the various functional assays described above. Briefly, carbohydrate-specific chemistry for biotinylation is used to confine a biotin tag to an albumin fusion protein of the invention, thus allowing uniform orientation upon immobilization. A 50uM solution of an albumin fusion protein of the invention in washed membranes is incubated with 20 mM NaIO4 and 1.5 mg/ml (4mM) BACH or 2 mg/ml (7.5mM) biotin-hydrazide for 1 hr at room temperature (reaction volume, 150ul). Then the sample is dialyzed (Pierce Slidealizer Cassett, 10 kDa cutoff; Pierce Chemical Co., Rockford IL) at 4C first for 5 h, exchanging the buffer after each hour, and finally for 12 h against 500 ml buffer R (0.15 M NaCl, 1 mM MgCl2, 10 mM sodium phosphate, pH7). Just before addition into a cuvette, the sample is diluted 1:5 in buffer ROG50 (Buffer R supplemented with 50 mM octylglucoside).

***EXAMPLE 55: Assays for Metalloproteinase Activity.***

**[1177]** Metalloproteinases are peptide hydrolases which use metal ions, such as $Zn^{2+}$, as the catalytic mechanism. Metalloproteinase activity of an albumin fusion protein of the present invention can be assayed according to methods known in the art. The following exemplary methods are provided:

*Proteolysis of alpha-2-macroglobulin*

**[1178]** To confirm protease activity, a purified fusion protein of the invention is mixed with the substrate alpha-2-macroglobulin (0.2 unit/ml; Boehringer Mannheim, Germany) in 1x assay buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 μM $ZnCl_2$ and 0.05% Brij-35) and incubated at 37°C for 1-5 days. Trypsin is used as positive control. Negative controls contain only alpha-2-macroglobulin in assay buffer. The samples are collected and boiled in SDS-PAGE sample buffer containing 5% 2-mercaptoethanol for 5-min, then loaded onto 8% SDS-polyacrylamide gel. After electrophoresis the proteins are visualized by silver staining. Proteolysis is evident by the appearance of lower molecular weight bands as compared to the negative control.

*Inhibition of alpha-2-macroglobulin proteolysis by inhibitors of metalloproteinases*

**[1179]** Known metalloproteinase inhibitors (metal chelators (EDTA, EGTA, AND $HgCl_2$), peptide metalloproteinase inhibitors (TIMP-1 and TIMP–2), and commercial small molecule MMP inhibitors) may also be used to characterize the proteolytic activity of an albumin fusion protein of the invention. Three synthetic MMP inhibitors that may be used are: MMP inhibitor I, [$IC_{50}$ = 1.0 μM against MMP-1 and MMP–8; $IC_{50}$ = 30 μM against MMP-9; $IC_{50}$ = 150 μM against MMP-3]; MMP-3 (stromelysin-1) inhibitor I [$IC_{50}$ = 5 μM against MMP-3], and MMP-3 inhibitor II [$K_i$ = 130 nM against MMP-3]; inhibitors available through Calbiochem, catalog # 444250, 444218, and 444225, respectively). Briefly, different concentrations of the small molecule MMP inhibitors are mixed with a purified fusion protein of the invention (50μg/ml) in 22.9 μl of 1x HEPES buffer (50 mM HEPES, pH 7.5, 0.2 M NaCl, 10 mM $CaCl_2$, 25 μM $ZnCl_2$ and 0.05%Brij-35) and incubated at room temperature (24 °C) for 2-hr, then 7.1 μl of substrate alpha-2-macroglobulin (0.2 unit/ml) is added and incubated at 37°C for 20-hr. The reactions are stopped by adding 4x sample buffer and boiled immediately for 5 minutes. After SDS-PAGE, the protein bands are visualized by silver stain.

*Synthetic Fluorogenic Peptide Substrates Cleavage Assay*

**[1180]** The substrate specificity for fusion proteins of the invention with demonstrated metalloproteinase activity may be determined using techniques knonw in the art, such as using synthetic fluorogenic peptide substrates (purchased from BACHEM Bioscience Inc). Test substrates include, M-1985, M-2225, M-2105, M-2110, and M-2255. The first four are MMP substrates and the last one is a substrate of tumor necrosis factor-α (TNF-α) converting enzyme (TACE). These substrastes are preferably prepared in 1:1 dimethyl sulfoxide (DMSO) and water. The stock solutions are 50-500 μM. Fluorescent assays are performed by using a Perkin Elmer LS

50B luminescence spectrometer equipped with a constant temperature water bath. The excitation λ is 328 nm and the emission λ is 393 nm. Briefly, the assay is carried out by incubating 176 µl 1x HEPES buffer (0.2 M NaCl, 10 mM $CaCl_2$, 0.05% Brij-35 and 50 mM HEPES, pH 7.5) with 4 µl of substrate solution (50 µM) at 25 °C for 15 minutes, and then adding 20 µl of a purified fusion protein of the invention into the assay cuvett. The final concentration of substrate is 1 µM. Initial hydrolysis rates are monitored for 30-min.

***EXAMPLE 56: Occurrence of Diabetes in NOD Mice.***

**[1181]** Female NOD (non-obese diabetic) mice are characterized by displaying IDDM with a course which is similar to that found in humans, although the disease is more pronounced in female than male NOD mice. Hereinafter, unless otherwise stated, the term "NOD mouse" refers to a female NOD mouse. NOD mice have a progressive destruction of beta cells which is caused by a chronic autoimmune disease. Thus, NOD mice begin life with euglycemia, or normal blood glucose levels. By about 15 to 16 weeks of age, however, NOD mice start becoming hyperglycemic, indicating the destruction of the majority of their pancreatic beta cells and the corresponding inability of the pancreas to produce sufficient insulin. Thus, both the cause and the progression of the disease are similar to human IDDM patients.

**[1182]** *In vivo* assays of efficacy of the immunization regimens can be assessed in female NOD/LtJ mice (commercially available from The Jackson Laboratory, Bar Harbor, Me.). In the literature, it's reported that 80% of female mice develop diabetes by 24 weeks of age and onset of insulitis begins between 6-8 weeks age. NOD mice are inbred and highly responsive to a variety of immunoregulatory strategies. Adult NOD mice (6-8 weeks of age) have an average mass of 20-25 g.

**[1183]** These mice can be either untreated (control), treated with the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof), alone or in combination with other therapeutic compounds stated above. The effect of these various treatments on the progression of diabetes can be measured as follows:

**[1184]** At 14 weeks of age, the female NOD mice can be phenotyped according to glucose tolerance. Glucose tolerance can be measured with the intraperitoneal glucose tolerance test (IPGTT). Briefly, blood is drawn from the paraorbital plexus at 0 minutes and 60 minutes after the intraperitoneal injection of glucose (1 g/kg body weight). Normal tolerance is defined as plasma glucose at 0 minutes of less than 144 mg %, or at 60 minutes of less than 160 mg %. Blood glucose levels are determined with a Glucometer Elite apparatus.

**[1185]** Based upon this phenotypic analysis, animals can be allocated to the different

experimental groups. In particular, animals with more elevated blood glucose levels can be assigned to the impaired glucose tolerance group. The mice can be fed ad libitum and can be supplied with acidified water (pH 2.3).

**[1186]** The glucose tolerant and intolerant mice can be further subdivided into control, albumin fusion proteins of the subject invention, and albumin fusion proteins/therapeutic compounds combination groups. Mice in the control group can receive an interperitoneal injection of vehicle daily, six times per week. Mice in the albumin fusion group can receive an interperitoneal injection of the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof) in vehicle daily, six times per week. Mice in the albumin fusion proteins/therapeutic compounds combination group can receive both albumin fusion proteins and combinations of therapeutic compounds as described above.

**[1187]** The level of urine glucose in the NOD mice can be determined on a bi-weekly basis using Labstix (Bayer Diagnostics, Hampshire, England). Weight and fluid intake can also be determined on a bi-weekly basis. The onset of diabetes is defined after the appearance of glucosuria on two consecutive determinations. After 10 weeks of treatment, an additional IPGTT can be performed and animals can be sacrificed the following day.

**[1188]** Over the 10 week course of treatment, control animals in both the glucose tolerant and glucose intolerant groups develop diabetes at a rate of 60% and 86%, respectively (see US patent No. 5,866,546, Gross et al.). Thus, high rates of diabetes occur even in NOD mice which are initially glucose tolerant if no intervention is made.

**[1189]** Results can be confirmed by the measurement of blood glucose levels in NOD mice, before and after treatment. Blood glucose levels are measured as described above in both glucose tolerant and intolerant mice in all groups described.

**[1190]** In an alternative embodiment, the therapeutics of the subject invention (e.g., specific fusions disclosed as SEQ ID NO:Y and fragments and variants thereof) can be quantified using spectrometric analysis and appropriate protein quantities can be resuspended prior to injection in 50 .mu.l phosphate buffered saline (PBS) per dose. Two injections, one week apart, can be administered subcutaneously under the dorsal skin of each mouse. Monitoring can be performed on two separate occasions prior to immunization and can be performed weekly throughout the treatment and continued thereafter. Urine can be tested for glucose every week (Keto-Diastix.RTM.; Miles Inc., Kankakee, Ill.) and glycosuric mice can be checked for serum glucose (ExacTech.RTM., MediSense, Inc., Waltham, Mass.). Diabetes is diagnosed when fasting glycemia is greater than 2.5g/L.

***EXAMPLE 57: Histological Examination of NOD Mice.***

**[1191]** Histological examination of tissue samples from NOD mice can demonstrate the ability of the compositions of the present invention, and/or a combination of the compositions of the present invention with other therapeutic agents for diabetes, to increase the relative concentration of beta cells in the pancreas. The experimental method is as follows:

**[1192]** The mice from Example 56 can be sacrificed at the end of the treatment period and tissue samples can be taken from the pancreas. The samples can be fixed in 10% formalin in 0.9% saline and embedded in wax. Two sets of 5 serial 5 .mu.m sections can be cut for immunolabelling at a cutting interval of 150 .mu.m. Sections can be immunolabelled for insulin (guinea pig anti-insulin antisera dilution 1:1000, ICN Thames U.K.) and glucagon (rabbit anti-pancreatic glucagon antisera dilution 1:2000) and detected with peroxidase conjugated anti-guinea pig (Dako, High Wycombe, U.K.) or peroxidase conjugated anti-rabbit antisera (dilution 1:50, Dako).

**[1193]** The composition of the present invention may or may not have as strong an effect on the visible mass of beta cells as it does on the clinical manifestations of diabetes in glucose tolerant and glucose intolerant animals.

***EXAMPLE 58: In vivo Mouse Model of NIDDM.***

**[1194]** Male C57BL/6J mice from Jackson Laboratory (Bar Harbor, ME) can be obtained at 3 weeks of age and fed on conventional chow or diets enriched in either fat (35.5% wt/wt; Bioserv.Frenchtown, NJ) or fructose (60% wt/wt; Harlan Teklad, Madison, WI). The regular chow is composed of 4.5% wt/wt fat, 23% wt/wt protein, 31.9% wt/wt starch, 3.7% wt/wt fructose, and 5.3% wt/wt fiber. The high-fat (lard) diet is composed of 35.5% wt/wt fat, 20% wt/wt protein, 36.4% wt/wt starch, 0.0% wt/wt fructose, and 0.1% wt/wt fiber. The high-fructose diet is composed of 5% wt/wt fat, 20% wt/wt protein, 0.0% wt/wt starch, 60% wt/wt fructose, and 9.4% wt/wt fiber. The mice may be housed no more than five per cage at 22° +/- 3°C temperature- and 50% +/- 20% humidity-controlled room with a 12-hour light (6 am to 6 pm)/dark cycle (Luo et al., 1998, Metabolism 47(6): 663-8, "Nongenetic mouse models of non-insulin-dependent diabetes mellitus"; Larsen et al., Diabetes 50(11): 2530-9 (2001), "Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats"). After exposure to the respective diets for 3 weeks, mice can be injected intraperitoneally with either streptozotocin, "STZ" (Sigma, St. Louis, MO), at 100 mg/kg body weight or vehicle (0.05 mol/L citric acid, pH 4.5) and kept on the same diet for the next 4 weeks. Under nonfasting conditions, blood is obtained 1, 2, and 4 weeks post-STZ by

nipping the distal part of the tail. Samples are used to measure nonfasting plasma glucose and insulin concentrations. Body weight and food intake are recorded weekly.

**[1195]** To directly determine the effect of the high-fat diet on the ability of insulin to stimulate glucose disposal, the experiments can be initiated on three groups of mice, fat-fed, chow-fed injected with vehicle, and fat-fed injected with STZ at the end of the 7-week period described above. Mice can be fasted for 4 hours before the experiments. In the first series of experiments, mice can be anesthetized with methoxyflurane (Pitman-Moor, Mundelein, IL) inhalation. Regular insulin (Sigma) can be injected intravenously ([IV] 0.1 U/kg body weight) through a tail vein, and blood can be collected 3, 6, 9, 12, and 15 minutes after the injection from a different tail vein. Plasma glucose concentrations can be determined on these samples, and the half-life (t½) of glucose disappearance from plasma can be calculated using WinNonlin (Scientific Consulting, Apex, NC), a pharmacokinetics/pharmacodynamics software program.

**[1196]** In the second series of experiments, mice can be anesthetized with intraperitoneal sodium pentobarbital (Sigma). The abdominal cavity is opened, and the main abdominal vein is exposed and catheterized with a 24-gauge IV catheter (Johnson-Johnson Medical, Arlington, TX). The catheter is secured to muscle tissue adjacent to the abdominal vein, cut on the bottom of the syringe connection, and hooked to a prefilled PE50 plastic tube, which in turn is connected to a syringe with infusion solution. The abdominal cavity is then sutured closed. With this approach, there would be no blockage of backflow of the blood from the lower part of the body. Mice can be infused continuously with glucose (24.1 mg/kg/min) and insulin (10 mU/kg/min) at an infusion volume of 10 μL/min. Retro-orbital blood samples (70 μL each) can be taken 90, 105, 120, and 135 minutes after the start of infusion for measurement of plasma glucose and insulin concentrations. The mean of these four samples is used to estimate steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations for each animal.

**[1197]** Finally, experiments to evaluate the ability of the albumin fusion proteins, the therapeutic compositions of the instant application, either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus, to decrease plasma glucose can be performed in the following two groups of "NIDDM" mice models that are STZ-injected: (1) fat-fed C57BL/6J, and (2) fructose-fed C57BL/6J. Plasma glucose concentrations of the mice for these studies may range from 255 to 555 mg/dL. Mice are randomly assigned to treatment with either vehicle, albumin fusion therapeutics of the present invention either alone or in combination with any one or more of the therapeutic drugs listed for the treatment of diabetes mellitus. A total of three doses can be administered. Tail vein blood samples can be taken for measurement of the

plasma glucose concentration before the first dose and 3 hours after the final dose.

**[1198]** Plasma glucose concentrations can be determined using the Glucose Diagnostic Kit from Sigma (Sigma No. 315), an enzyme colorimetric assay. Plasma insulin levels can be determined using the Rat Insulin RIA Kit from Linco Research (#RI-13K; St. Charles, MO).

***EXAMPLE 59: In vitro H4IIe –SEAP Reporter Assays Establishing Involvement in Insulin Action.***

*The Various H4IIe Reporters*

**[1199]** *H4IIe/rMEP-SEAP*: The malic enzyme promoter isolated from rat (rMEP) contains a PPAR-gamma element which is in the insulin pathway. This reporter construct is stably transfected into the liver H4IIe cell-line.

**[1200]** *H4IIe/SREBP-SEAP*: The sterol regulatory element binding protein (SREBP-1c) is a transcription factor which acts on the promoters of a number of insulin-responsive genes, for example, fatty acid synthetase (FAS), and which regulates expression of key genes in fatty acid metabolism in fibroblasts, adipocytes, and hepatocytes. SREBP-1c, also known as the adipocyte determination and differentiation factor 1 (ADD-1), is considered as the primary mediator of insulin effects on gene expression in adipose cells. It's activity is modulated by the levels of insulin, sterols, and glucose. This reporter construct is stably transfected into the liver H4IIe cell-line.

**[1201]** *H4IIe/FAS-SEAP*: The fatty acid synthetase reporter constructs contain a minimal SREBP-responsive FAS promoter. This reporter construct is stably transfected into the liver H4IIe cell-line.

**[1202]** *H4IIe/PEPCK-SEAP*: The phosphoenolpyruvate carboxykinase (PEPCK) promoter is the primary site of hormonal regulation of PEPCK gene transcription modulating PEPCK activity. PEPCK catalyzes a committed and rate-limiting step in hepatic gluconeogenesis and must therefore be carefully controlled to maintain blood glucose levels within normal limits. This reporter construct is stably transfected into the liver H4IIe cell-line.

**[1203]** These reporter constructs can also be stably transfected into 3T3-L1 fibroblasts and L6 myoblasts. These stable cell-lines are then differentiated into 3T3-L1 adipocytes and L6 myotubes as previously described in Example 13. The differentiated cell-lines can then be used in the SEAP assay described below.

*Growth and Assay Medium*

**[1204]** The growth medium comprises 10% Fetal Bovine Serum (FBS), 10% Calf Serum, 1% NEAA, 1x penicillin/streptomycin, and 0.75 mg/mL G418 (for H4IIe/rFAS-SEAP and

H4IIe/SREBP-SEAP) or 0.50 mg/mL G418 (for H4IIe/rMEP-SEAP). For H4IIe/PEPCK-SEAP, the growth medium consists of 10% FBS, 1% penicillin/streptomycin, 15 mM HEPES buffered saline, and 0.50 mg/mL G418.

**[1205]** The assay medium consists of low glucose DMEM medium (Life Technologies), 1% NEAA, 1x penicillin/streptomycin for the H4IIe/rFAS-SEAP, H4IIe/SREBP-SEAP, H4IIe/rMEP-SEAP reporters. The assay medium for H4IIe/PEPCK-SEAP reporter consists of 0.1% FBS, 1% penicillin/streptomycin, and 15 mM HEPES buffered saline.

*Method*

**[1206]** The 96-well plates are seeded at 75,000 cells/well in 100 μL/well of growth medium until cells in log growth phase become adherent. Cells are starved for 48 hours by replacing growth medium with assay medium, 200 μL/well. (For H4IIe/PEPCK-SEAP cells, assay medium containing 0.5 μM dexamethasone is added at 100 μL/well and incubated for approximately 20 hours). The assay medium is replaced thereafter with 100 μL/well of fresh assay medium, and a 50 μL aliquot of cell supernatant obtained from transfected cell-lines expressing the therapeutics of the subject invention (e.g., albumin fusion proteins of the invention and fragments and variants thereof) is added to the well. Supernatants from empty vector transfected cell-lines are used as negative control. Addition of 10 nM and/or 100 nM insulin to the wells is used as positive control. After 48 hours of incubation, the conditioned media are harvested and SEAP activity measured (Phospha-Light System protocol, Tropix #BP2500). Briefly, samples are diluted 1:4 in dilution buffer and incubated at 65 °C for 30 minutes to inactivate the endogenous non-placental form of SEAP. An aliquot of 50 μL of the diluted samples is mixed with 50 μL of SEAP Assay Buffer which contains a mixture of inhibitors active against the non-placental SEAP isoenzymes and is incubated for another 5 minutes. An aliquot of 50 μL of CSPD chemiluminescent substrate which is diluted 1:20 in Emerald luminescence enhancer is added to the mixture and incubated for 15-20 minutes. Plates are read in a Dynex plate luminometer.

***EXAMPLE 60: Transgenic Animals.***

**[1207]** The albumin fusion proteins of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express fusion proteins of the invention in humans, as part of a gene therapy protocol.

**[1208]** Any technique known in the art may be used to introduce the polynucleotides encoding

the albumin fusion proteins of the invention into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

**[1209]** Any technique known in the art may be used to produce transgenic clones containing polynucleotides encoding albumin fusion proteins of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

**[1210]** The present invention provides for transgenic animals that carry the polynucleotides encoding the albumin fusion proteins of the invention in all their cells, as well as animals which carry these polynucleotides in some, but not all their cells, *i.e.,* mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.,* head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide encoding the fusion protein of the invention be integrated into the chromosomal site of the endogenous gene corresponding to the Therapeutic protein portion or ablumin portion of the fusion protein of the invention, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the

endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

**[1211]** Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the polynucleotide encoding the fsuion protien of the invention has taken place. The level of mRNA expression of the polynucleotide encoding the fusion protein of the invention in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of fusion protein-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the fusion protein.

**[1212]** Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene (i.e., polynucleotide encoding an albumin fusion protein of the invention) on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of fusion proteins of the invention and the Therapeutic protein and/or albumin component of the fusion protein of the invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

***EXAMPLE 61: Method of Treatment Using Gene Therapy-Ex Vivo.***

**[1213]** One method of gene therapy transplants fibroblasts, which are capable of expressing an

albumin fusion protein of the present invention, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

**[1214]** At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

**[1215]** pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

**[1216]** Polynucleotides encoding an albumin fusion protein of the invention can be generated using techniques known in the art amplified using PCR primers which correspond to the 5' and 3' end sequences and optionally having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

**[1217]** The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

**[1218]** Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells

and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether the albumin fusion protein is produced.

**[1219]** The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

***EXAMPLE 62: Method of Treatment Using Gene Therapy - In Vivo.***

**[1220]** Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences encoding an albumin fusion protein of the invention into an animal. Polynucleotides encoding albumin fusion proteins of the present invention may be operatively linked to (i.e., associated with) a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

**[1221]** The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

**[1222]** The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, polynucleotides encoding albumin fusion proteins of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

**[1223]** The polynucleotide vector constructs used in the gene therapy method are preferably

constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

**[1224]** The polynucleotide construct can be delivered to the interstitial space of tissues within an animal, including muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

**[1225]** For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

**[1226]** The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

**[1227]** Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

**[1228]** After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for fusion protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

***EXAMPLE 63: Biological Effects of Fusion Proteins of the Invention.***

*Astrocyte and Neuronal Assays.*

**[1229]** Albumin fusion proteins of the invention can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an albumin fusion protein of the invention's activity on these cells.

**[1230]** Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated

hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA 83*:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an albumin fusion protein of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

*Fibroblast and endothelial cell assays.*

**[1231]** Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test fusion protein of the invention proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the $PGE_2$ assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or fusion protein of the invention with or without IL-1α for 24 hours. The supernatants are collected and assayed for $PGE_2$ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without an albumin fusion protein of the invention and/or IL-1α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

**[1232]** Human lung fibroblasts are cultured with FGF-2 or an albumin fusion protein of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with the fusion protein of the invention.

*Cell proliferation based on [3H]thymidine incorporation*

**[1233]** The following [3H]Thymidine incorporation assay can be used to measure the effect of a Therapeutic proteins, e.g., growth factor proteins, on the proliferation of cells such as fibroblast

cells, epithelial cells or immature muscle cells.

**[1234]** Sub-confluent cultures are arrested in G1 phase by an 18 h incubation in serum-free medium. Therapeutic proteins are then added for 24 h and during the last 4 h, the cultures are labeled with [3H]thymidine, at a final concentration of 0.33 μM (25 Ci/mmol, Amersham, Arlington Heights, IL). The incorporated [3H]thymidine is precipitated with ice-cold 10% trichloroacetic acid for 24 h. Subsequently, the cells are rinsed sequentially with ice-cold 10% trichloroacetic acid and then with ice-cold water. Following lysis in 0.5 M NaOH, the lysates and PBS rinses (500 ml) are pooled, and the amount of radioactivity is measured.

*Parkinson Models.*

**[1235]** The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine ($MPP^+$) and released. Subsequently, $MPP^+$ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. $MPP^+$ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

**[1236]** It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

**[1237]** Based on the data with FGF-2, an albumin fusion protein of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an albumin fusion protein of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/$cm^2$ on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium

containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

**[1238]** Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a therapeutic protein of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the fusion protein may be involved in Parkinson's Disease.

***EXAMPLE 64: Pancreatic Beta-Cell Transplantation Combination Therapy.***

**[1239]** Transplantation is a common form of treatment of autoimmune disease, especially when the target self tissue has been severely damaged. For example, and not by way of limitation, pancreas transplantation and islet cell transplantation are common treatment options for IDDM (See, e.g., Stewart et al., Journal of Clinical Endocrinology & Metabolism 86 (3): 984-988 (2001); Brunicardi, Transplant. Proc. 28: 2138-40 (1996); Kendall & Robertson, Diabetes Metab. 22: 157-163 (1996); Hamano et al., Kobe J. Med. Sci. 42: 93-104 (1996); Larsen & Stratta, Diabetes Metab. 22: 139-146 (1996); and Kinkhabwala, et al., Am. J. Surg. 171: 516-520 (1996)). As with any transplantation method, transplantation therapies for autoimmune disease patients include treatments to minimize the risk of host rejection of the transplanted tissue. However, autoimmune disease involves the additional, independent risk that the pre-existing host autoimmune response which damaged the original self tissue will exert the same damaging effect on the transplanted tissue. Accordingly, the present invention encompasses methods and compositions for the treatment of autoimmune pancreatic disease using the albumin fusion proteins of the subject invetion in combination with immunomodulators/immunosuppressants in individuals undergoing transplantation therapy of the autoimmune disease.

**[1240]** In accordance with the invention, the albumin fusion-based compositions and formulations described above, are administered to prevent and treat damage to the transplanted organ, tissue, or cells resulting from the host individual's autoimmune response initially directed against the original self tissue. Administration may be carried out both prior and subsequent to transplantation in 2 to 4 doses each one week apart.

**[1241]** The following immunomodulators/immunosuppressants including, but not limited to, AI-401, CDP-571 (anti-TNF monoclonal antibody), CG-1088, Diamyd (diabetes vaccine), ICM3 (anti-ICAM-3 monoclonal antibody), linomide (Roquinimex), NBI-6024 (altered peptide ligand), TM-27, VX-740 (HMR-3480), caspase 8 protease inhibitors, thalidomide, hOKT3gamma1 (Ala-ala) (anti-CD3 monoclonal antibody), Oral Interferon-Alpha, oral lactobacillus, and LymphoStat-B™ can be used together with the albumin fusion therapeutics of the subject invention in islet cell or pancreas transplantation.

***EXAMPLE 65:Identification and Cloning of VH and VL domains.***

**[1242]** One method to identfy and clone VH and VL domains from cell lines expressing a particular antibody is to perform PCR with VH and VL specific primers on cDNA made from the antibody expressing cell lines. Briefly, RNA is isolated from the cell lines and used as a template for RT-PCR designed to amplify the VH and VL domains of the antibodies expressed by the EBV cell lines. Cells may be lysed in the TRIzol® reagent (Life Technologies, Rockville. MD) and extracted with one fifth volume of chloroform. After addition of chloroform, the solution is allowed to incubate at room temperature for 10 minutes, and the centrifuged at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. The supernatant is collected and RNA is precipitated using an equal volume of isopropanol. Precipitated RNA is pelleted by centrifuging at 14,000 rpm for 15 minutes at 4°C in a tabletop centrifuge. Following centrifugation, the supernatant is discarded and washed with 75% ethanol. Follwing washing, the RNA is centrifuged again at 800 rpm for 5 minutes at 4°C. The supernatant is discarded and the pellet allowed to air dry. RNA is the dissolved in DEPC water and heated to 60°C for 10 minutes. Quantities of RNA can determined using optical density measurements.

**[1243]** cDNA may be synthesized, according to methods well-known in the art, from 1.5-2.5 micrograms of RNA using reverse transciptase and random hexamer primers. cDNA is then used as a template for PCR amplification of VH and VL domains. Primers used to amplify VH and VL genes are shown in Table 7. Typically a PCR reaction makes use of a single 5' primer and a single 3' primer. Sometimes, when the amount of available RNA template is limiting, or for greater efficiency, groups of 5' and/or 3' primers may be used. For example, sometimes all five VH-5' primers and all JH3' primers are used in a single PCR reaction. The PCR reaction is carried out in a 50 microliter volume containing 1X PCR buffer, 2mM of each dNTP, 0.7 units of High Fidelity Taq polymerse, 5' primer mix, 3' primer mix and 7.5 microliters of cDNA. The 5' and 3' primer mix of both VH and VL can be made by pooling together 22 pmole and 28 pmole, respectively, of each of the individual primers. PCR conditions are: 96°C for 5 minutes;

followed by 25 cycles of 94°C for 1 minute, 50°C for 1 minute, and 72°C for 1 minute; followed by an extension cycle of 72°C for 10 minutes. After the reaction is completed, sample tubes are stored 4°C.

**Table 7: Primer Sequences Used to Amplify VH and VL domains.**

| Primer name | SEQ ID NO | Primer Sequence (5'-3') |
|---|---|---|
| *VH Primers* | | |
| Hu VH1-5' | 62 | CAGGTGCAGCTGGTGCAGTCTGG |
| Hu VH2-5' | 63 | CAGGTCAACTTAAGGGAGTCTGG |
| Hu VH3-5' | 64 | GAGGTGCAGCTGGTGGAGTCTGG |
| Hu VH4-5' | 65 | CAGGTGCAGCTGCAGGAGTCGGG |
| Hu VH5-5' | 66 | GAGGTGCAGCTGTTGCAGTCTGC |
| Hu VH6-5' | 67 | CAGGTACAGCTGCAGCAGTCAGG |
| Hu JH1,2-5' | 68 | TGAGGAGACGGTGACCAGGGTGCC |
| Hu JH3-5' | 69 | TGAAGAGACGGTGACCATTGTCCC |
| Hu JH4,5-5' | 70 | TGAGGAGACGGTGACCAGGGTTCC |
| Hu JH6-5' | 71 | TGAGGAGACGGTGACCGTGGTCCC |
| *VL Primers* | | |
| Hu Vkappa1-5' | 72 | GACATCCAGATGACCCAGTCTCC |
| Hu Vkappa2a-5' | 73 | GATGTTGTGATGACTCAGTCTCC |
| Hu Vkappa2b-5' | 74 | GATATTGTGATGACTCAGTCTCC |
| Hu Vkappa3-5' | 75 | GAAATTGTGTTGACGCAGTCTCC |
| Hu Vkappa4-5' | 76 | GACATCGTGATGACCCAGTCTCC |
| Hu Vkappa5-5' | 77 | GAAACGACACTCACGCAGTCTCC |
| Hu Vkappa6-5' | 78 | GAAATTGTGCTGACTCAGTCTCC |
| Hu Vlambda1-5' | 79 | CAGTCTGTGTTGACGCAGCCGCC |
| Hu Vlambda2-5' | 80 | CAGTCTGCCCTGACTCAGCCTGC |
| Hu Vlambda3-5' | 81 | TCCTATGTGCTGACTCAGCCACC |
| Hu Vlambda3b-5' | 82 | TCTTCTGAGCTGACTCAGGACCC |
| Hu Vlambda4-5' | 83 | CACGTTATACTGACTCAACCGCC |
| Hu Vlambda5-5' | 84 | CAGGCTGTGCTCACTCAGCCGTC |
| Hu Vlambda6-5' | 85 | AATTTTATGCTGACTCAGCCCCA |
| Hu Jkappa1-3' | 86 | ACGTTTGATTTCCACCTTGGTCCC |
| Hu Jkappa2-3' | 87 | ACGTTTGATCTCCAGCTTGGTCCC |
| Hu Jkappa3-3' | 88 | ACGTTTGATATCCACTTTGGTCCC |

| | | |
|---|---|---|
| Hu Jkappa4-3' | 89 | ACGTTTGATCTCCACCTTGGTCCC |
| Hu Jkappa5-3' | 90 | ACGTTTAATCTCCAGTCGTGTCCC |
| Hu Jlambda1-3' | 91 | CAGTCTGTGTTGACGCAGCCGCC |
| Hu Jlambda2-3' | 92 | CAGTCTGCCCTGACTCAGCCTGC |
| Hu Jlambda3--3' | 93 | TCCTATGTGCTGACTCAGCCACC |
| Hu Jlambda3b-3' | 94 | TCTTCTGAGCTGACTCAGGACCC |
| Hu Jlambda4-3' | 95 | CACGTTATACTGACTCAACCGCC |
| Hu Jlambda5-3' | 96 | CAGGCTGTGCTCACTCAGCCGTC |
| Hu Jlambda6-3' | 97 | AATTTTATGCTGACTCAGCCCCA |

PCR samples are then electrophoresed on a 1.3% agarose gel. DNA bands of the expected sizes (~506 base pairs for VH domains, and 344 base pairs for VL domains) can be cut out of the gel and purified using methods well known in the art. Purified PCR products can be ligated into a PCR cloning vector (TA vector from Invitrogen Inc., Carlsbad, CA). Individual cloned PCR products can be isolated after transfection of E. coli and blue/white color selection. Cloned PCR products may then be sequenced using methods commonly known in the art.

**[1244]** The PCR bands containing the VH domain and the VL domains can also be used to create full-length Ig expression vectors. VH and VL domains can be cloned into vectors containing the nucleotide sequences of a heavy (e.g., human IgG1 or human IgG4) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods using polynucleotides encoding VH and VL antibody domain to generate expression vectors that encode complete antibody molecules are well known within the art.

***EXAMPLE 66: Preparation of HA-cytokine or HA-growth factor fusion proteins (such as NGF, BDNFa, BDNFb and BDNFc).***

**[1245]** The cDNA for the cytokine or growth factor of interest, such as NGF, can be isolated by a variety of means including from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning

of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. NGF (or other cytokine) cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines, a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 67: Preparation of HA-IFN fusion proteins (such as IFNα).***

**[1246]** The cDNA for the interferon of interest such as IFNα can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for interferons, such as IFNα are known and available, for instance, in U.S. Patents 5,326,859 and 4,588,585, in EP 32 134, as well as in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used to clone the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus of the HA sequence, with or without the use of a spacer sequence. The IFNα (or other interferon) cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

*Maximum protein recovery from vials*

**[1247]** The albumin fusion proteins of the invention have a high degree of stability even when they are packaged at low concentrations. In addition, in spite of the low protein concentration, good fusion-protein recovery is observed even when the aqueous solution includes no other protein added to minimize binding to the vial walls. The recovery of vial-stored HA-IFN solutions was compared with a stock solution. 6 or 30 μg/ml HA-IFN solutions were placed in

vials and stored at 4°C. After 48 or 72 hrs a volume originally equivalent to 10 ng of sample was removed and measured in an IFN sandwich ELISA. The estimated values were compared to that of a high concentration stock solution. As shown, there is essentially no loss of the sample in these vials, indicating that addition of exogenous material such as albumin is not necessary to prevent sample loss to the wall of the vials

*In vivo stability and bioavailability of HA-α-IFN fusions*

**[1248]** To determine the in vivo stability and bioavailability of a HA-α-IFN fusion molecule, the purified fusion molecule (from yeast) was administered to monkeys. Pharmaceutical compositions formulated from HA-α-IFN fusions may account for the extended serum half-life and bioavailability. Accordingly, pharmaceutical compositions may be formulated to contain lower dosages of alpha-interferon activity compared to the native alpha-interferon molecule.

**[1249]** Pharmaceutical compositions containing HA-α-IFN fusions may be used to treat or prevent disease in patients with any disease or disease state that can be modulated by the administration of α-IFN. Such diseases include, but are not limited to, hairy cell leukemia, Kaposi's sarcoma, genital and anal warts, chronic hepatitis B, chronic non-A, non-B hepatitis, in particular hepatitis C, hepatitis D, chronic myelogenous leukemia, renal cell carcinoma, bladder carcinoma, ovarian and cervical carcinoma, skin cancers, recurrent respirator papillomatosis, non-Hodgkin's and cutaneous T-cell lymphomas, melanoma, multiple myeloma , AIDS, multiple sclerosis, gliobastoma, etc. (see Interferon Alpha, In: AHFS Drug Information, 1997.

**[1250]** Accordingly, the invention includes pharmaceutical compositions containing a HA-α-IFN fusion protein, polypeptide or peptide formulated with the proper dosage for human administration. The invention also includes methods of treating patients in need of such treatment comprising at least the step of administering a pharmaceutical composition containing at least one HA-α-IFN fusion protein, polypeptide or peptide.

*Bifunctional HA-□-IFN fusions*

**[1251]** A HA-α-IFN expression vector may be modified to include an insertion for the expression of bifunctional HA-α-IFN fusion proteins. For instance, the cDNA for a second protein of interest may be inserted in frame downstream of the "rHA-IFN" sequence after the double stop codon has been removed or shifted downstream of the coding sequence.

**[1252]** In one version of a bifunctional HA-α-IFN fusion protein, an antibody or fragment against B-lymphocyte stimulator protein (GenBank Acc 4455139) or polypeptide may be fused to one end of the HA component of the fusion molecule. This bifunctional protein is useful for modulating any immune response generated by the α-IFN component of the fusion.

***EXAMPLE 68: Preparation of HA-hormone fusion protein***

**[1253]** The cDNA for the hormone of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The hormone cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 69: Preparation of HA-soluble receptor or HA-binding protein fusion protein.***

**[1254]** The cDNA for the soluble receptor or binding protein of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The receptor cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 70: Preparation of HA-growth factors.***

**[1255]** The cDNA for the growth factor of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods (see GenBank Acc. No.NP_000609). The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The growth factor cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 71: Preparation of HA-single chain antibody fusion proteins.***

**[1256]** Single chain antibodies are produced by several methods including but not limited to: selection from phage libraries, cloning of the variable region of a specific antibody by cloning the cDNA of the antibody and using the flanking constant regions as the primer to clone the variable region, or by synthesizing an oligonucleotide corresponding to the variable region of any specific antibody. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The cell cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast.

**[1257]** In fusion molecules of the invention, the $V_H$ and $V_L$ can be linked by one of the following means or a combination thereof: a peptide linker between the C-terminus of the $V_H$ and the N-terminus of the $V_L$; a Kex2p protease cleavage site between the $V_H$ and $V_L$ such that the two are cleaved apart upon secretion and then self associate; and cystine residues positioned such that the $V_H$ and $V_L$ can form a disulphide bond between them to link them together. An alternative option would be to place the $V_H$ at the N-terminus of HA or an HA domain fragment and the $V_L$ at the C-terminus of the HA or HA domain fragment.

**[1258]** The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines. The antibody produced in this manner can be purified from media and tested for its binding to its antigen using standard immunochemical methods.

***EXAMPLE 72: Preparation of HA-cell adhesion molecule fusion proteins.***

**[1259]** The cDNA for the cell adhesion molecule of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. . The nucleotide sequences for the known cell adhesion molecules are known and available, for instance, in GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The cell adhesion molecule cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 73: Preparation of inhibitory factors and peptides as HA fusion proteins (such as HA-antiviral, HA-antibiotic, HA-enzyme inhibitor and HA-anti-allergic proteins).***

**[1260]** The cDNA for the peptide of interest such as an antibiotic peptide can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The peptide cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA from

which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 74: Preparation of targeted HA fusion proteins.***

**[1261]** The cDNA for the protein of interest can be isolated from cDNA library or can be made synthetically using several overlapping oligonucleotides using standard molecular biology methods. The appropriate nucleotides can be engineered in the cDNA to form convenient restriction sites and also allow the attachment of the protein cDNA to albumin cDNA. Also a targeting protein or peptide cDNA such as single chain antibody or peptides, such as nuclear localization signals, that can direct proteins inside the cells can be fused to the other end of albumin. The protein of interest and the targeting peptide is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA , or pC4:HSA which allows the fusion with albumin cDNA. In this manner both N- and C-terminal end of albumin are fused to other proteins. The fused cDNA is then excised from pPPC0005 and is inserted into a plasmid such as pSAC35 to allow the expression of the albumin fusion protein in yeast. All the above procedures can be performed using standard methods in molecular biology. The albumin fusion protein secreted from yeast can be collected and purified from the media and tested for its biological activity and its targeting activity using appropriate biochemical and biological tests.

***EXAMPLE 75: Preparation of HA-enzymes fusions.***

**[1262]** The cDNA for the enzyme of interest can be isolated by a variety of means including but not exclusively, from cDNA libraries, by RT-PCR and by PCR using a series of overlapping synthetic oligonucleotide primers, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for HA. This can be at the N or C-terminus with or without the use of a spacer sequence. The enzyme cDNA is cloned into a vector such as pPPC0005 (Figure 2), pScCHSA, pScNHSA, or pC4:HSA from which the complete expression cassette is then excised and inserted into the plasmid pSAC35 to allow the expression of the albumin fusion protein in yeast. The albumin fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For

expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator (See Example 1). This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

***EXAMPLE 76: Construct ID 2249, IFNa2-HSA, Generation.***

**[1263]** Construct ID 2249, pSAC35:IFNa2.HSA, comprises DNA encoding an IFNa2 albumin fusion protein which has the HSA chimeric leader sequence, followed by the mature form of IFNa2 protein, i.e., C1-E165, fused to the amino-terminus of the mature form of HSA in the yeast *S. cerevisiae* expression vector pSAC35.

*Cloning of IFNa2 cDNA*

**[1264]** The polynucleotide encoding IFNa2 was PCR amplified using primers IFNa2-1 and IFNa2-2, described below. The PCR amplimer was cut with *Sal I/Cla* I, and ligated into *Xho I/Cla* I cut pScCHSA. Construct ID #2249 encodes an albumin fusion protein containing the chimeric leader sequence of HSA, the mature form of IFNa2, followed by the mature HSA protein.

**[1265]** Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the mature form of IFNa2, IFNa2-1 and IFNa2-2, were synthesized:

IFNa2-1: 5'-CGCGCGCGTCGACAAAAGATGTGATCTGCCTCAAACCCACA-3' (SEQ ID NO:348)

IFNa2-2:
5'-GCGCGCATCGATGAGCAACCTCACTCTTGTGTGCATCTTCCTTACTTCTTAAACTTTCT-3' (SEQ ID NO:349)

**[1266]** The IFNa2-1 primer incorporates a *Sal* I cloning site (shown underlined), nucleotides encoding the last three amino acid residues of the chimeric HSA leader sequence, as well as 22 nucleotides (shown in bold) encoding the first 7 amino acid residues of the mature form of IFNa2. In IFNa2-2, the *Cla* I site (shown underlined) and the DNA following it are the reverse complement of DNA encoding the first 10 amino acids of the mature HSA protein and the last 22 nucleotides (shown in bold) are the reverse complement of DNA encoding the last 7 amino acid residues of IFNa2 (see Example 2). A PCR amplimer of IFNa2-HSA was generated using these primers, purified, digested with *Sal* I and *Cla* I restriction enzymes, and cloned into the *Xho* I and *Cla* I sites of the pScCHSA vector. After the sequence was confirmed, the expression cassette encoding this IFNa2 albumin fusion protein was subcloned into *Not* I digested pSAC35.

**[1267]** Further, analysis of the N-terminus of the expressed albumin fusion protein by amino acid

sequencing can confirm the presence of the expected IFNa2 sequence (see below).

**[1268]** Other IFNa2 albumin fusion proteins using different leader sequences have been constructed by methods known in the art (see Example 2). Examples of the various leader sequences include, but are not limited to, invertase "INV" (constructs 2343 and 2410) and mating alpha factor "MAF" (construct 2366). These IFNa2 albumin fusion proteins can be subcloned into mammalian expression vectors such as pC4 (constructs 2382) and pEE12.1 as described previously (see Example 5). IFNa2 albumin fusion proteins with the therapeutic portion fused C-terminus to HSA can also be constructed (construct 2381).

**[1269]** IFNa2 albumin fusion proteins of the invention preferably comprise the mature form of HSA , i.e., Asp-25 to Leu-609, fused to either the N- or C- terminus of the mature form of IFNa2, i.e., Cys-1 to Glu-165. In one embodiment of the invention, IFNa2 albumin fusion proteins of the invention further comprise a signal sequence which directs the nascent fusion polypeptide in the secretory pathways of the host used for expression. In a further preferred embodiment, the signal peptide encoded by the signal sequence is removed, and the mature IFNa2 albumin fusion protein is secreted directly into the culture medium. IFNa2 albumin fusion proteins of the invention may comprise heterologous signal sequences including, but not limited to, MAF, INV, Ig, Fibulin B, Clusterin, Insulin-Like Growth Factor Binding Protein 4, variant HSA leader sequences including, but not limited to, a chimeric HSA/MAF leader sequence, or other heterologous signal sequences known in the art. In a preferred embodiment, IFNa2 albumin fusion proteins of the invention comprise the native IFNa2. In further preferred embodiments, the IFNa2 albumin fusion proteins of the invention further comprise an N-terminal methionine residue. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

*Expression and Purification of Construct ID 2249.*

*Expression in yeast S. cerevisiae.*

**[1270]** Transformation of construct 2249 into yeast *S. cerevisiae* strain BXP10 was carried out by methods known in the art (see Example 3). Cells can be collected at stationary phase after 72 hours of growth. Supernatants are collected by clarifying cells at 3000g for 10 min. Expression levels are examined by immunoblot detection with anti-HSA serum (Kent Laboratories) or as the primary antibody. The IFNa2 albumin fusion protein of approximate molecular weight of 88.5 kDa can be obtained.

*Purification from yeast S. cerevisiae cell supernatant.*

**[1271]** The cell supernatant containing IFNa2 albumin fusion protein expressed from construct

ID #2249 in yeast *S. cerevisiae* cells can be purified either small scale over a Dyax peptide affinity column (see Example 4) or large scale by following 5 steps: diafiltration, anion exchange chromatography using DEAE-Sepharose Fast Flow column, hydrophobic interaction chromatography (HIC) using Butyl 650S column, cation exchange chromatography using an SP-Sepharose Fast Flow column or a Blue-Sepharose chromatography, and high performance chromatography using Q-sepharose high performance column chromatography (see Example 4). The IFNa2 albumin fusion protein may elute from the DEAE-Sepharose Fast Flow column with 100 – 250 mM NaCl, from the SP-Sepharose Fast Flow column with 150 – 250 mM NaCl, and from the Q-Sepharose High Performance column at 5 – 7.5 mS/cm. N-terminal sequencing should yield the sequence CDLPQ (SEQ ID NO:98) which corresponds to the mature form of IFNa2.

*The activity of IFNa2 can be assayed using an in vitro ISRE-SEAP assay.*

*Method*

**[1272]** The IFNa2 albumin fusion protein encoded by construct ID # 2249 can be tested for activity in the ISRE-SEAP assay as previously described in Example 76. Briefly, conditioned yeast supernatants were tested at a 1:1000 dilution for their ability to direct ISRE signal transduction on the ISRE-SEAP/293F reporter cell-line. The ISRE-SEAP/293F reporter cells were plated at 3 x $10^4$ cell/well in 96-well, poly-D-lysine coated, plates, one day prior to treatment. The reporter cells were then incubated for 18 or 24 hours prior to removing 40 µL for use in the SEAP Reporter Gene Chemiluminescent Assay (Roche catalog # 1779842). Recombinant human Interferon beta, "rhIFNb" (Biogen), was used as a positive control.

*Result*

**[1273]** The purified preparation of IFNa2-HSA demonstrated a relatively linear increase in the ISRE-SEAP assay over concentrations ranging from $10^{-1}$ to $10^{1}$ ng/mL (see Figure 4) or $10^{-10}$ to $10^{-8}$ ng/mL (see Figure 5).

*In vivo induction of OAS by Interferon alpha fusion encoded by construct ID 2249.*

*Method*

**[1274]** The OAS enzyme, 2'-5'- OligoAdenylate Synthetase, is activated at the transcriptional level by interferon in response to antiviral infection. The effect of interferon constructs can be measured by obtaining blood samples from treated monkeys and analyzing these samples for transcriptional activation of two OAS mRNA, p41 and p69. A volume of 0.5 mL of whole blood was obtained from 4 animals per group at 7 different time points, day 0, day 1, day 2, day 4, day 8, day 10, and day 14 per animal. The various groups include vehicle control, intravenous

injection of 30 μg/kg HSA-IFN on day 1, subcutaneous injection of 30 μg/kg of HSA-IFN on day 1, subcutaneous injection of 300 μg/kg of HSA-IFN on day 1, and subcutaneous injection of 40 μg/kg of Interferon alpha (Schering-Plough) as a positive control on days 1, 3, and 5. The levels of the p41 and the p69 mRNA transcripts were determined by real-time quantitative PCR (Taqman) using probes specific for p41-OAS and p69-OAS. OAS mRNA levels were quantitated relative to 18S ribosomal RNA endogenous control. The albumin fusion encoded by construct 2249 can be subjected to similar experimentation.

*Results*

**[1275]** A significant increase in mRNA transcript levels for both p41 and p69 OAS was observed in HSA-interferon treated monkeys in contrast to IFNa treated monkeys (see Figure 6 for p41 data). The effect lasted nearly 10 days.

***EXAMPLE 77: Indications for IFNa2 Albumin Fusion Proteins.***

**[1276]** IFN alpha albumin fusion protein (including, but not limited to, those encoded by constructs 2249, 2343, 2410, 2366, 2382, and 2381) can be used to treat, prevent, ameliorate, and/or detect multiple sclerosis. Other indications include, but are not limited to viral infections including Severe Acute Respiratory Syndrome (SARS) and other coronavirus infections; filoviruses, including but not limited to Ebola viruses and Marburg virus; Arenaviruses, including but not limited to Pichende virus, Lassa virus, Junin virus, Machupo virus, Guanarito virus; and lymphocytic choriomeningitis virus (LCMV); Bunyaviruses, including but not limited to Punta toro virus, Crimean-Congo hemorrhagic fever virus, sandfly fever viruses, Rift Valley fever virus, La Crosse virus, and hantaviruses; Flaviviruses, including but not limited to Yellow Fever, Banzi virus, West Nile virus, Dengue viruses, Japanese Encephalitis virus, Tick-borne encephalitis, Omsk Hemorrhagic Fever, and Kyasanur Forest Disease virus; Togaviruses, including but not limited to Venezuelan, eastern, and western equine encephalitis viruses, Ross River virus, and Rubella virus; Orthopox viruses, including but not limited to Vaccinia, Cowpox, Smallpox, and Monkeypox; Herpesviruses; FluA/B; Respiratory Sincytial virus (RSV); paraflu; measles; rhinoviruses; adenoviruses; Semliki Forest virus; Viral Hemorrhagic fevers; Rhabdoviruses; Paramyxoviruses, including but not limited to Nipah virus and Hendra virus; and other viral agents identified by the U.S. Centers for Disease Control and Prevention as high-priority disease agents (*i.e.*, Category A, B, and C agents; see, *e.g.*, Moran, Emerg. Med. Clin. North. Am. 2002; 20(2):311-30 and Darling et al., Emerg. Med. Clin. North Am. 2002;20(2):273-309).

**[1277]** Preferably, the IFNα-albumin fusion protein or IFN hybrid fusion protein is administered in combination with a CCR5 antagonist, further in association with at least one of ribavirin, IL-2,

IL-12, pentafuside alone or in combination with an anti-HIV drug therapy, e.g., HAART, for preparation of a medicament for the treatment of HIV-1 infections, HCV, or HIV-1 and HCV co-infections in treatment-naïve as well as treatment-experienced adult and pediatric patients.

***Example 78: Construct ID # 3691, BNP-HSA, Generation.***

**[1278]** Construct ID # 3691, pC4:SPCON.BNP1-32/HSA, comprises DNA encoding a BNP albumin fusion protein which has a consensus leader sequence, secrecon, followed by the processed, active BNP peptide (amino acids 1-32) fused to the amino-terminus of the mature form of HSA in the mammalian expression vector pC4.

*Cloning of BNP cDNA for construct 3691*

**[1279]** The polynucleotide encoding BNP was PCR amplified using primers BNP-1 and BNP-2, described below, cut with *Bam* HI/*Cla* I, and ligated into *Bam* HI/*Cla* I cut pC4:HSA resulting in construct ID # 3691. Construct ID # 3691 encodes an albumin fusion protein containing a consensus leader sequence (SEQ ID No:111) and the processed, active form of BNP, followed by the mature HSA protein (see SEQ ID NO:204 for construct 3691 in Table 2).

**[1280]** Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the active, processed form of BNP, BNP-1 and BNP-2, were synthesized:

BNP-1: 5'-

GAGCGCGGATCCAAGCTTCCGCCATC*ATGTGGTGGCGCCTGTGGTGGCT GCTGCTGCTGCTGCTGCTGCTGTG GCCCATGGTGTGGGCC*AGCCCCAAGCTGGTGCAAGG -3' (SEQ ID NO:364)

BNP-2: 5'-

AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATCATGCCGCCTCAGCACTTTGC-3' (SEQ ID NO:365).

**[1281]** BNP-1 incorporates a *Bam* HI cloning site (underlined), polynucleotides encoding a consensus leader sequence (SEQ ID NO:111) (italicized), and polynucleotides encoding the first seven amino acid sequence of BNP (bolded). In BNP-2, the underlined sequence is a *Cla* I site, and the polynucleotides that follow it contains the reverse complement of DNA encoding the last 6 amino acids of BNP (bolded) and the first 10 amino acids of the mature HSA protein. Using these two primers the BNP protein was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

**[1282]** The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bam* HI and *Cla* I. After further purification of

the *Bam* HI-*Cla* I fragment by gel electrophoresis, the product was cloned into *Bam* HI /*Cla* I digested pC4:HSA to produce construct ID # 3691. The expression construct was sequence verified.

*Expression and Purification of Construct ID* 3691.

*Expression in 293F cells.*

**[1283]** Construct ID # 3691, pC4:SPCON.BNP1-32/HSA, was transfected into 293F cells by methods known in the art (see Example 6).

*Purification from 293F cell supernatant.*

**[1284]** Two liters of supernatant were collected 3 days post-transfection. The recombinant protein was captured by 5 ml Blue Sepharose CL-6B column (Amersham Biosciences, Piscataway, NJ, USA) and eluted by 2 M NaCl. The material was bound to HiPrep 16/10 Phenyl FF (high sub) column and eluted by 20 mM MES, pH 6.7. BNP-HSA was further purified by hydroxyapatite column chromatography in sodium phosphate buffer gradient (0–20 mS/cm in 200 ml) at pH 6.8. The final product was exchanged into PBS pH 7.2 by a HiPrep 26/10 desalting column (Amersham Biosciences).

*The activity of BNP-HSA can be assayed using an in vitro NPR-A/cGMP Assay.*

**[1285]** Natriuretic peptide receptor-A (NPR-A) is the signaling receptor for BNP, and as such, is responsible for most of BNP's biological effects. BNP bioactivity is mediated by NPR-A guanylyl cyclase domain that converts GTP to cGMP upon activation. A convenient assay for BNP activity is to measure the BNP stimulation of a 293F cell line that stably over-expresses NPR-A. The cGMP production in the cells after exposure to BNP can be measured by cGMP ELISA.

*Method of Screening NPR-A 293F stable clones.*

**[1286]** The open reading frame of human NPR-A was constructed into pcDNA3.1 expression vector (Invitrogen). 293F cells were stably transfected with the plasmid DNA by Lipofectamine method and selected by 0.8 μg/ml G418. 293F/NPR-A stable clones were screened for best response to recombinant BNP.

*Measurement of cGMP activation.*

**[1287]** cGMP activation by BNP was carried out in 293F/NPR-A cells and measured by CatchPoint cyclic-GMP fluorescent assay kit (Molecular Devices, Sunnyvale, CA, USA). Briefly, 50,000 cells/well of 293F/NPR-A cells cultured in a 96-well plate were washed into 80 μl prestimulation buffer (Krebs-Ringer Bicarbonate Buffer with 10 mM glucose, pH 7.4, 15 nM sodium bicarbonate, and 0.75 mM 3-isobutyl-1-methylxanthine). BNP-HSA or recombinant

BNP in 40 µl prestimulation buffer was added to the cells at 37°C for 10 min. The cells were lysed with 40 µl Lysis Buffer for 10 min with shaking. The amounts of cGMP in the lysates were quantitated as per the manufacturer's instruction.

*Result*

**[1288]** The dose-response relationship of BNP-HSA and recombinant BNP were determined (see Figure 7). The maximal activities of Construct ID # 3691 and recombinant BNP were similar (1.63 ± 0.016 vs. 1.80 ± 0.016 pm, respectively), with EC50 values of 28.4 ± 1.2, and 0.46 ± 1.1 nM, respectively.

*BNP-HSA decreases blood pressure in vivo.*

*Method*

**[1289]** BNP reduces blood pressure by direct vasodilation as well as by suppression of renin/angiotensin/endothelin/aldosterone systems. The ability of BNP-HSA to decrease arterial blood pressure was tested in three-month old male spontaneously hypertensive rats purchased from Taconic (Germantown, NY, USA). Spontaneously hypertensive rats are genetically hypertensive with onset of high blood pressure after three months of age. BNP-HSA or recombinant BNP was reconstituted in 0.3 cc PBS per rat. The drugs were delivered via tail vein injection. Systolic and diastolic blood pressures were recorded by cuff-tail method using XBP-1000 System (Kent Scientific, Torrington, CT, USA). For each blood pressure data point, 4-5 consecutive readings were taken and averaged. Mean arterial pressure (MAP) was calculated as 1/3 systolic pressure + 2/3 diastolic pressure. For dose-response determination, blood pressures were measured 20 h after pC4:SPCON.BNP1-32/HSA administration at doses of 0.5, 2, 6, and 18 nmol/kg.

*Result*

**[1290]** The typical systolic pressure of spontaneously hypertensive rats was 180–200 mmHg before dosing. A single bolus of 6 nmol/kg BNP-HSA delivered via tail vein intravenous injection lowered both systolic and diastolic pressure, which accounted for more than 30 mmHg mean arterial pressure (MAP) reduction. The lowered blood pressure was steady and continued for a day and then gradually returned to the baseline over several days (see Figure 8). In contrast, due to its instantaneous clearance, a single 6 nmol/kg bolus of recombinant BNP, produced only a very transient MAP decrease of about ~15 mmHg.

**[1291]** In addition, the dose-response 20 hours post injection of a bolus of BNP-HSA was determined in four spontaneously hypertensive rats. 0.5 nmol/kg BNP-HSA had an average of 7 mmHg MAP reduction, while 6 nmol/kg BNP-HSA had an average of 30 mmHg MAP reduction,

and a high dose of 18 nmol/kg BNP-HSA only lowered the blood pressure slightly more than 6 nmol/kg.

*In vivo induction of plasma cGMP by BNP-HSA.*

*Method*

**[1292]** The intracellular cGMP activation by BNP results in its release from the cell to circulation. The plasma cGMP level correlates with BNP-induced cardiovascular and renal physiology. Plasma cGMP has been used as a biomarker for *in vivo* BNP action. To test the induction of plasma cGMP by BNP-HSA *in vivo*, eleven- to 12-week-old male C57/BL6 mice received a single bolus of recombinant BNP or BNP-HSA at a 6 nmol/kg dose via tail vein. Plasma was prepared from the tail bleeds at 5, 10, 20, 40, and 80 min time points for the recombinant BNP dosing group and at additional 640, 1440, 2880, and 5760 min for the BNP-HSA group. Plasma samples from mice treated with PBS as the vehicle control were collected as the zero time points. cGMP levels were determined by CatchPoint cyclic-GMP fluorescent assay kit according to the manufacture's instruction.

*Result*

**[1293]** Following a single intravenous bolus of 6 nmol/kg recombinant BNP or BNP-HSA, peak plasma cGMP levels over the baseline were increased 3.9- or 5.6-fold, respectively (see Figure 9). In addition, the one-phase exponential decay half-life of cGMP following recombinant BNP treatment was 16 min (10 to 42 min, 95%CI), while the one-phase exponential decay half-life of cGMP following BNP-HSA administration was 1538 min (1017 to 3153 min, 95%CI).

*In vivo Pharmacokinetic analysis of BNP albumin fusion encoded by construct ID* 3691.

*Method*

**[1294]** Eleven- to 12-week-old male C57/BL6 mice (obtained from Ace Animals, Boyertown, PA, USA) weighed 25.1 ± 0.12 g at the time of the study. All animals were dosed at a volume of 10 ml/kg body weight. Predose animals were injected with PBS. Recombinant BNP was injected intravenously in the tail or subcutaneously in the mid-scapular region.

**[1295]** Pharmacokinetic analysis was performed on the following groups:

**Table 8.**

| Group | Drug | Dose (mg/kg) | Route | N/time | Time (hours) |
|---|---|---|---|---|---|
| 1 | BNP-HSA | 2.19 | Subcutaneous | 3 | 0.5, 2, 6, 16, 24, 32, 48, 72, 96 |
| 2 | BNP-HSA | 2.19 | Intravenous | 3 | 0.083, 2, 6, 16, 24, 32, 48, 72, 96 |
| 3 | Vehicle | 0 | Subcutaneous | 3 | predose |
| 4 | Vehicle | 0 | Intravenous | 3 | predose |

**[1296]** Blood was sampled from the inferior vena cava, placed into an EDTA-coated microtainer, and stored on ice. The samples were centrifuged in a microcentrifuge at 14,000 rpm (16,000 ×*g*) for 10 minutes at room temperature. The plasma was transferred into cluster tubes and stored at –80°C.

**[1297]** BNP-HSA concentrations in plasma samples were determined using BNP EIA Kit (Phoenix Pharmaceutical, Belmont, CA, USA). The standard curves were generated at the same time on the same plate with testing samples. The detection limit was 0.11 ng/mL for recombinant BNP. The assay detects recombinant BNP and does not cross react to mouse BNP.

**[1298]** Analysis was conducted by noncompartmental methods (WinNonlin; version 4.1; Pharsight Corp.,Mountain View, CA, USA). The mean plasma concentration at each time was used in the analysis. A linear up/log down trapezoidal method was used to calculate the $AUC0_{-t}$. Extrapolation to infinity $AUC_{0-\infty}$ was done by dividing the last observed concentration by the terminal elimination rate constant. Data were uniformly weighted for these analyses.

*Result*

**[1299]** The mean baseline concentration of BNP-HSA in plasma as detected in the pre-dose samples was approximately 0.081–0.095 μg/ml. Following a single intravenous or subcutaneous injection, BNP-HSA had terminal elimination half-lives of 11.2 (intravenous delivery) or 19.3 h (subcutaneous delivery), while the half-life of recombinant BNP in mice was 3.1 min. Non compartmental analysis of BNP-HSA revealed that BNP-HSA had the following characteristics:

**Table 9.**

| | Unit | Intravenous | Subcutaneous |
|---|---|---|---|
| $t_{max}$ | h | NA | 16 |
| $C_{max}$ | μg/ml | NA | 11.2 |
| $t_{1/2,term}$ | h | 11.2 | 19.3 |
| $AUC_{0-\infty}$ | (h · μg/ml)/(mg/kg) | 658.9 | 227.9 |
| $V_{ss}$ | ml/kg | 37 | NA |
| $V_z$ or $V_z/F$ | ml/kg | 53.5 | 268 |
| CL or CL/F | ml/h/kg | 3.3 | 9.6 |
| MRT | h | 11.2 | 19.8 |
| Bioavailability | % | | 34.6 |
| | | | |

| |
|---|
| $C_{max}$, peak plasma concentration of the drug; $t_{max}$, time of maximum plasma concentration; $AUC_{0-\infty}$, area under the plasma drug concentration-time curve from time 0 to infinite time; $t_{1/2,term}$, terminal elimination phase half-life; CL, clearance after intravenous dosing; CL/F, apparent clearance after subcutaneous dosing; $V_{ss}$, volume of distribution at steady-state after intravenous dosing; $V_z$: volume of distribution during the terminal phase after intravenous dosing; $V_z/F$, volume of distribution during the terminal phase after subcutaneous dosing; NA, not applicable. |

**[1300]** Five points at the terminal phase of the intravenous profile and four points at the terminal phase of the subcutaneous profile were selected for the terminal half-life calculation. The resulting AUC during this terminal phase was approximately 10% of the total AUC for the intravenous and subcutaneous profiles, respectively. This is compared to only 2% and 4% of the total AUC for the intravenous and subcutaneous profile, respectively, when the last three points were selected for the terminal half-life calculation.

***EXAMPLE 79: Construct ID # 3618, BNP(2X)-HSA, Generation.***

**[1301]** Construct ID # 3618, pC4:SPCON.BNP1-32(2x)/HSA, comprises DNA encoding a BNP albumin fusion protein which has a consensus leader sequence, secreton, followed by two processed, active BNP peptides (amino acids 1-32) in tandem fused to the amino-terminus of the mature form of HSA in the mammalian expression vector pC4.

*Cloning of BNP cDNA for construct 3618*

**[1302]** The polynucleotide encoding the duplicate BNP moiety was first PCR amplified from the processed active form of BNP (amino acids 1-32) using four primers BNP-1, BNP-2, BNP-3, and BNP-4, described below, to create two fragments A and B. Following amplification, two purified fragments (A and B) were mixed in an equal molar amount and used as a PCR template and amplified with primers BNP-5 and BNP-6, as described below. The BNP(2X) insert was then digested with *Bam*HI and *Cla*I and ligated into pC4HSA vector pre-digested with *Bam*HI and *Cla*I resulting in construct 3618. Construct ID # 3618 encodes an albumin fusion protein containing a consensus leader sequence, secrecon (SEQ ID NO:111), and two, tandem copies of the processed, active form of BNP, followed by the mature HSA protein (see SEQ ID NO:226 for construct 3618 in Table 2).

**[1303]** Four oligonucleotides suitable for PCR amplification of the polynucleotides encoding two fragments of BNP protein were first synthesized:

BNP-1 5'-

AGCCCCAAGATGGTGCAAGGGTCTGGCTGCTTTGGGAGGAAGATGGAC

CGGATCA GCTCCTCCAGTG GCTGGGCT GCAAAGTGCTGAGGCGGCAT-3' (SEQ ID NO:460)

BNP-2 5'-CCTTGCACCATCTTGGGGCTATGCCGCCTCAGCACTTTGC-3' (SEQ ID NO:461)

BNP-3 5'-GCAAAGTGCTGAGGCGGCATAGCCCCAAGATGGTGCAAGG-3' (SEQ ID NO:462)

BNP-4 5'-AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATCATGCCGCCTC AGCACTTTGC-3' (SEQ ID NO:463)

**[1304]** Using primer sets BNP-1/BNP-2 and BNP-3/BNP-4, two BNP proteins fragments (A and B, respectively) were PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template. Fragments A and B were purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)), mixed at equal molar amounts, and used as a template for PCR amplification using two additional oligonucleotides suitable for PCR amplification, BNP-5 and BNP-6:

BNP-5: 5'-GAGCGCGGATCCAAGCTTCCGCCATC*ATGTGGTGGCGCCTGTGGTGGCT GCTGC TGCTCTGCTGCTGCT GTGGCCCATGGTGTGGGCC*AGCCCCAAGCTGGTGCAAGG -3' (SEQ ID NO:382)

BNP-6: 5'-AGTCCCATCGATGAGCAACCTCACTCTTGTGTGCATCATGCCGCCTCAGCACTTTGC-3' (SEQ ID NO:383)

**[1305]** BNP-5 incorporates a *Bam* HI cloning site (underlined), polynucleotides encoding a consensus leader sequence (SEQ ID No:111) (italicized), and polynucleotides encoding the first seven amino acid sequence of BNP (bolded). In BNP-6, the underlined sequence is a *Cla* I site, and the polynucleotides that follow it contains the reverse complement of DNA encoding the last 6 amino acids of BNP (bolded) and the first 10 amino acids of the mature HSA protein. Using these two primers, a consensus leader sequence and two tandem copies of active BNP peptides were PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

**[1306]** The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bam* HI and *Cla* I. After further purification of

the *Bam* HI-*Cla* I fragment by gel electrophoresis, the product was cloned into *Bam* HI /*Cla* I digested pC4:HSA to produce construct ID # 3618. The expression construct was sequence verified.

*Expression and Purification of Construct ID # 3618.*

*Expression in 293F cells.*

**[1307]** Construct ID # 3618, pC4:SPCON.BNP1-32(2x)/HSA, was transfected into 293F cells by methods known in the art (see Example 6).

*Purification from 293F cell supernatant.*

**[1308]** pC4:SPCON.BNP1-32(2x)/HSA encoded by Construct ID # 3618 was purified as previously described above in Example 78 under subsection heading "Purification from 203F cell supernatant."

*The Activity of BNP(2X)-HSA can be assayed using an In Vitro NPR-A/cGMP Assay.*

**[1309]** The activity of BNP(2X)-HSA encoded by Construct ID # 3618 can be assayed *in vitro* using an NPR-A/cGMP assay as previously described in Example 78 under subsection heading, "The activity of BNP-HSA can be assayed using an in vitro NPR-A/cGMP Assay," and "Method of Screening NPR-A 203F Stable Clones."

*Result*

The dose-response relationship of BNP(2X)-HSA and recombinant BNP were determined (see Figure 7). The maximal activities of BNP(2X)-HSA encoded by Construct ID # 3618, and recombinant BNP were similar (1.68 ± 0.021, vs. 1.80 ± 0.016 pm, respectively), with EC50 values of 9.8 ± 1.1, and 0.46 ± 1.1 nM respectively.

***Example 80: In vitro NPR-A/cGMP Assay for BNP.***

*Background and Methods*:

**[1310]** Natriuretic peptide receptor-A (NPR-A) is the signaling receptor for BNP, and as such, is responsible for most of BNP's biological effects. BNP bioactivity is mediated by NPR-A guanylyl cyclase domain that converts GTP to cGMP upon activation. A convenient assay for BNP activity is to measure the BNP stimulation of a 293F cell line that stably over-expresses NPR-A. The cGMP production in the cells after exposure to BNP can be measured by cGMP ELISA.

*Method of Screening NPR-A 293F stable clones.*

**[1311]** The open reading frame of human NPR-A was constructed into pcDNA3.1 expression vector (Invitrogen). 293F cells were stably transfected with the plasmid DNA by Lipofectamine method and selected by 0.8 μg/ml G418. 293F/NPR-A stable clones were screened for best

response to recombinant BNP.

*Measurement of cGMP activation.*

**[1312]** cGMP activation by BNP was carried out in 293F/NPR-A cells and measured by CatchPoint cyclic-GMP fluorescent assay kit (Molecular Devices, Sunnyvale, CA, USA). Briefly, 50,000 cells/well of 293F/NPR-A cells cultured in a 96-well plate were washed into 80 µl prestimulation buffer (Krebs-Ringer Bicarbonate Buffer with 10 mM glucose, pH 7.4, 15 nM sodium bicarbonate, and 0.75 mM 3-isobutyl-1-methylxanthine). BNP-HSA or recombinant BNP in 40 µl prestimulation buffer was added to the cells at 37°C for 10 min. The cells were lysed with 40 µl Lysis Buffer for 10 min with shaking. The amounts of cGMP in the lysates were quantitated as per the manufacturer's instruction and EC50 values were determined. In this assay, higher cGMP levels result in lower signals (relative fluorescent units or RFUs).

*Generation of Construct ID # 3796*

**[1313]** Construct ID # 3796, pSAC35:HSA.BNP(1-32), comprises DNA encoding a BNP albumin fusion protein which has a HSAsp/KEX2 leader sequence, followed by the processed, mature form of HSA, fused to the N-terminus of the procecessed, mature form of BNP peptide (amino acids 1-32) in the yeast expression vector pSAC35 (see SEQ ID NO:214 for construct 3796 in Table 2).

*Cloning of BNP cDNA for construct 3796*

**[1314]** The polynucleotide encoding BNP was PCR amplified using primers BNP-102689 and BNP-102692, described below, cut with *Bsu36I/AscI*, and ligated into *Bsu36I/AscI*, cut pSAC-NEC resulting in construct ID # 3796. The template for PCR amplification was polynucleotides encoding the entire mature BNP (1-32 sequence).

**[1315]** Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the active, processed form of BNP, BNP-102689 and BNP-102692 were synthesized:

BNP-102689: 5'-AAGCTG*CCTTAGGCTTA*AGCCCCAAGATGGTGCAAGGGTC-3'
(SEQ ID NO:378)

BNP-102692: 5'-GCACCGGGCGCGCC*TTA*ATGCCGCCTCAGCACTTTGCAGC-3'
(SEQ ID NO:379)

**[1316]** BNP-102689 incorporates a *Bsu36I* cloning site (underlined), polynucleotides encoding the last five amino acids of HSA (italicized), and polynucleotides encoding the first eight amino acid sequence of BNP (bolded). In BNP-102692, the underlined sequence is a *Asc* I site, and the polynucleotides that follow it contains the reverse complement of DNA encoding the last 8 amino acids of BNP (bolded) and a termination codon (italicized). Using these two primers the

HSA/BNP fusion region was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

**[1317]** The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bsu36I* and Asc I. After further purification of the *Bsu36I* /Asc I fragment by gel electrophoresis, the product was cloned into *Bsu36I* /Asc I digested pSAC35-NEC to produce construct ID # 3796. The expression construct was sequence verified.

*Expression and Purification of Construct ID* 3796.

*Expression in S. cerevisiae.*

**[1318]** Construct ID # 3796, pSAC35:HSA.BNP(1-32), was transfected into BXP10 cells by methods known in the art (see Example 4).

*Purification from BXP10 cell supernatant.*

**[1319]** After approximately 84 hours, the culture was harvested and clarified of cells through centrifugation and 0.2μm filtration. The recombinant protein was captured by 5 ml Blue Sepharose fast flow column (GE Healthcare) and eluted by a combination of sodium chloride and sodium octanoate. Some preparation were completed by binding the protein to a ceramic hydoxyl appetite column (BioRad) and eluting with an increased concentration of phosphate. Other preparations were bound to a DEAE Sepharose fast flow column (GE Heathcare) and eluted by a linear sodium chloride gradient. The elution pool was then bound to a Q sepharose high performance column (GE Healthcare) and eluted with a sodium chloride gradient. The final product was concentrated and exhanged in formulation buffer by tangential flow filtration.

*Generation and Cloning of Construct ID # 3959*

**[1320]** Construct ID # 3959, pSAC35:HSA.BNP(1-29), comprises DNA encoding a BNP albumin fusion protein which has a HSAsp/KEX2 leader sequence, followed by the processed, mature form of HSA, fused to the N-terminus of the procecessed, mature form of BNP peptide lacking the last three amino acids (S1-L29) in the yeast expression vector pSAC35 (*see* SEQ ID NO:501 for construct 3959 in Table 2).

**[1321]** The polynucleotide encoding BNP was PCR amplified using primers BNP-103801 and BNP-104315, described below, cut with *Bsu36I/AscI*, and ligated into *Bsu36I/AscI*, cut pSAC-NEC resulting in construct ID # 3959. The template for PCR amplification was primer construct ID 3796 (see below).

**[1322]** Two oligonucleotides suitable for PCR amplification of the polynucleotide encoding the active, processed form of BNP, BNP-103801 and BNP-104315 were synthesized:

BNP-103801: 5'-

CAGGAGCC*CCTTAGGCTTA*AGCCCCAAGATGGTGCAAGGGTCT -3' (SEQ ID NO:578)

BNP-104315: 5'-

CCTCACTCGGCGCGCC*TTA*CAGCACTTTGCAGCCCAGGCCACTGGA -3' (SEQ ID NO:579)

**[1323]** BNP-103801 incorporates a *Bsu36I* cloning site (underlined), polynucleotides encoding the last five amino acids of HSA (italicized), and polynucleotides encoding the first eight amino acid sequence of BNP (bolded). In BNP-104315, the underlined sequence is a *Asc* I site, and the polynucleotides that follow it contains the reverse complement of DNA encoding the S21 through L29 amino acids of BNP (bolded) and a termination codon (italicized). Using these two primers the HSA/BNP fusion region was PCR amplified. Annealing and extension temperatures and times must be empirically determined for each specific primer pair and template.

**[1324]** The PCR product was purified (for example, using Wizard PCR Preps DNA Purification System (Promega Corp)) and then digested with *Bsu36I* and *Asc* I. After further purification of the *Bsu36I /Asc* I fragment by gel electrophoresis, the product was cloned into *Bsu36I /Asc* I digested pSAC35-NEC to produce construct ID # 3959. The expression construct was sequence verified.

*Expression and Purification of Construct ID 3959.*

*Expression in S. cerevisiae.*

**[1325]** Construct ID # 3959, pSAC35:HSA.BNP(S1-L29), was transfected into BXP10 cells by methods known in the art (see Example 4).

*Purification from BXP10 cell supernatant.*

**[1326]** After approximately 84 hours, the culture was harvested and clarified of cells through centrifugation and 0.2μm filtration. The recombinant protein was captured by 5 ml Blue Sepharose fast flow column (GE Healthcare) and eluted by a combination of sodium chloride and sodium octanoate. Some preparation were completed by binding the protein to a ceramic hydoxyl appetite column (BioRad) and eluting with an increased concentration of phosphate. Other preparations were bound to a DEAE Sepharose fast flow column (GE Heathcare) and eluted by a linear sodium chloride gradient. The elution pool was then bound to a Q sepharose high performance column (GE Healthcare) and eluted with a sodium chloride gradient. The final product was concentrated and exhanged in formulation buffer by tangential flow filtration.

*Result*

[1327] The dose-response relationship of HSA-BNP(1-29) and HSA-BNP(1-32) and recombinant BNP were determined (see Figure 10). The EC50 value of HSA-BNP(1-29) and HSA-BNP(1-32) were several fold greater than the EC50 value of recombinant BNP (467.9, 45.06, and 0.2227, respectively). In addition, the HSA-BNP(1-29) fusion protein had a 10 fold greater EC50 value than HSA-BNP(1-32) fusion protein.

***Example 81: In vitro Assay for Degradation of ANP and BNP.***

*Background and Methods*:

[1328] Neprilysin, also known as MME, CALLA, CD10, Common acute lymphocytic leukemia antigen, Enkephalinase, EPN, NEP, Neutral endopeptidase, or Neutral endopeptidase 24.11, is a 743 amino acid (MW 90,000-110,000 kD) cell-surface metallopeptidase expressed by numerous tissues, including, but not limited to, prostate, kidney, intestine, endometrium, adrenal glands, and lung. Neprilysin inactivates a variety of physiologically active peptides, including, but not limited to, ANP, BNP, CNP, substance P, bradykinin, oxytocin, Leu- and Met-enkephalins, neurotensin, bombesin, endothelin-1, and bombesin-like peptides, by cleaving the amino side of hydrophobic residues.

[1329] The relative susceptibility to neprilysin hydrolysis has been determined to be approximately 4-5 minutes for CNP, 8 minutes for ANP, and 2 hours for BNP. (Kenny, A.J. et al., Biochem J. 291(1): 83-8 (1993)).

*The Effect of Neprilysin on ANP and BNP Peptides*

[1330] ANP and BNP peptides were assayed for activity in the CatchPoint cGMP assay (Molecular Devises) with or without exposure to the protease neprilysin. Particuarly, 5 μM of ANP or BNP was incubated for 24 hours at 37°C in MES buffer (0.1M 2-(N-morpholino)ethanesulfonic acid (Sigma)) with or without 10nM neprilysin (R&D Systems). 293F cells, which have been stably transfected with NPR-A as described in Example 80, were then stimulated with various concentrations of protease-treated ANP or BNP. Cell lysates were then analyzed for cGMP activation using the CatchPoint cGMP assay (Molecular Devices) as described in Example 80.

*Results*

[1331] Dose-response curves were calculated for BNP and ANP with or without incubation with neprilysin. (See, Figure 11A). BNP with or without incubation with neprilysin exhibited similar BNP activity with EC50 values of 0.2966 and 0.2702, respectively. However, incubation of ANP with neprilysin resulted in a significant reduction in ANP activity compared to untreated ANP with EC50 values of 0.2965 and 60.47, respectively. Select samples were further analyzed

by reverse-phase HPLC, using techniques known in the art. Percent comparisons are to samples incubated for the same period of time in the absence of neprilysin. (See, Figure 11D) Although ANP proteolysis occurs within 20 minutes of treatment with neprilysin, significant BNP proteolysis is not observed even after 24 hours of incubation with neprilysin.

*The Effect of Neprilysin on ANP-HSA fusion proteins*

**[1332]** ANP and ANP-HSA (CID 3484) were incubated in MES buffer (0.1M 2-(N-morpholino)ethanesulfonic acid (Sigma)) with or without 10nM neprilysin (R&D Systems) for 20 minutes, 1 hour, or 24 hours at 37°C. 293F cells, which have been stably transfected with NPR-A as described in Example 80, were then stimulated with various concentrations of protease-treated ANP or ANP-HSA. Cell lysates were then analyzed for cGMP activation using the CatchPoint cGMP assay (Molecular Devices) as described in Example 80.

*Results*

**[1333]** Dose-response curves were calculated for ANP and ANP-HSA with or without incubation with neprilysin. (See, Figures 11B and 11C, respectively). ANP peptide demonstrated a significant reduction in activity within 1 hour of treatment with neprilysin. However, ANP-HSA (CID 3484) demonstrated no significant reduction in activity even after 24 hours of treatment with neprilysin. Select samples were further analyzed by reverse-phase HPLC, using techniques known in the art. Percent comparisons are to samples incubated for the same period of time in the absence of neprilysin. (See, Figure 11D). Although ANP proteolysis occurs within 20 minutes of treatment with neprilysin, no proteolysis of ANP-HSA (CID 3484) was observed even after 24 hours of incubation with neprilysin.

***Example 82: Anti-Viral Activity of HSA-IFNα2b, in Combination with Ribavirin in Genotype 1, Interferon-Naïve Chronic Hepatitis C (HCV) Patients***

*Background*:

**[1334]** Conventional treatment for Genotype 1, interferon-naïve (IFN-naïve) HCV patients utilizes interferon α in combination with ribavirin (RBV) for 48 weeks. However, this treatment has significant practical limitations. Due to the well-known side effects of current interferon therapy, patients' quality of life is substantially decreased after each administration of interferon. Current protocols require dosing at least weekly, resulting in a prolonged period of decreased quality of life. Large numbers of patients discontinue treatment as a result, with some studies reporting discontinuation rates over 50%. Moreover, current interferon therapy also has a considerable rate of significant hematological reductions, which can require a reduction in RBV dose, or more significantly, in a temporary termination of the interferon treatment regimen until

the hematological values normalize. Thus, there is a clear need for improved therapeutic protocols for the treatment of genotype 1 HCV in IFN-naïve patients.

*Rationale*:

**[1335]** HSA-IFNα2b was generated by genetically fusing mature albumin at its C-terminus to the N-terminus of mature interferon α-2b. The safety and efficacy of treatment with HSA-IFNα2b in combination with RBV was evaluated in an active controlled clinical study in genotype 1, IFN-naïve HCV human patients, and compared to conventional treatment with PEG-IFNα-2a (PEG-IFN) in combination with RBV as an active control.

*Methods*:

**[1336]** Human HCV patients who were genotype 1, IFN-naïve were treated with either HSA-IFNα2b or active control, PEG-IFN, in combination with ribavirin (RBV). More particularly, 458 human subjects were randomized into 4 subcutaneous (sc) treatment groups: (a) PEG-IFN dosed at 180 μg once weekly (Q1w); (b) HSA-IFNα2B dosed at 900 μg once every 2 weeks (Q2w); (c) HSA-IFNα2b dosed at 1200 μg Q2w; or (d) HSA-IFNα2b dosed at 1200 μg once every 4 weeks (Q4w)).

**[1337]** Each subject in each treatment group also received 1000-1200 mg/day RBV based on body weight. The basis for stratification included body mass index (BMI) (<25 kg/m$^2$ or ≥ 25 kg/m$^2$) and HCV RNA titer (<800,000 IU/ml or ≥ 800,000 IU/ml).

**[1338]** Treatment duration of the study is 48 weeks with a 24 week follow-up. The primary efficacy endpoint of the study is sustained virologic response (SVR).

**[1339]** HCV RNA titer was measured using a real-time PCR assay, Quantasure™ (Labcorp) with a sensitivity range (level of quantification (LOQ)) of 43 IU to 69 million IU/mL and a level of detection (LOD) of 10 IU/mL. Alanine Transferase (ALT) and hematologic effects, including absolute neutrophil count (ANC), hemoglobin, and platelet count were measured using standard techniques known in the art.

**[1340]** Intent to treat (ITT) patients are defined as all randomized and treated subjects of each treatment group, regardless of whether or not the patient has any missing data points or has dropped out of the study. Modified intent to treat (MITT) patients are defined as those patients that could conceivably have a Week 24 visit based on their date of enrollment in the study.

*Results and Discussion:*

**[1341]** Subject demographics, antiviral response and hematologic reductions are summarized in Table 10 (preliminary interim analysis) and Table 11 (final interim analysis). Overall, all four treatment protocols were well tolerated and there were no significant difference between the

treatment groups with respect to grade 3-4 lab values or discontinuations due to adverse events.

**Table 10.** *Preliminary Interim Analysis of Demographic, Anti-viral Response, and Hematological Effect*

| | PEG-IFN 180 μg Q1w (n=114) | HSA-IFNα2b 1200 μg Q2w (n=110) | HSA-IFNα2b 900 μg Q2w (n=118) | HSA-IFNα2b 1200 μg Q4w (n=116) |
|---|---|---|---|---|
| **Demographics** | | | | |
| Male | 58% | 58% | 55% | 67% |
| Mean BMI ($kg/m^2$) | 25.1 | 25.7 | 25.4 | 26.1 |
| • BMI ≥25 $kg/m^2$ | 53% | 49% | 49% | 51% |
| Median HCV RNA (log IU/ml) | 6.0 | 6.0 | 6.1 | 6.1 |
| • RNA ≥800,000 IU/ml | 62% | 55% | 56% | 62% |
| **Efficacy at Week 12** | | | | |
| HCV RNA Negative (<LOQ) | 70/112 (62.5%)[¶] | 77/104 (74.0%)[¶] | 74/112 (66.1%) | 57/109 (52.3%)* |
| • BMI <25 $kg/m^2$ vs. ≥25 $kg/m^2$ | 71.1% vs. 54.2% | 74.1% vs. 74.0% | 70.7% vs. 61.1% | 55.6% vs. 49.1% |
| EVR12 (≥2 log reduction) | 96/112 (85.7%) | 91/104 (87.5%) | 90/112 (80.4%) | 80/109 (73.4%) |
| $2^{nd}$ phase slope >0.6 log/wk | 49% | 58% | 52% | 42% |
| Normalization of ALT | 12/73 (16.4%) | 17/80 (21.2%) | 18.81 (22.2%) | 27/83 (32.5%)[#] |
| **Laboratory at Week 12** | | | | |
| ANC<750/$mm^3$ | 17.5% | 20.0% | 22.0% | 4.3%** |
| ANC<500/ $mm^3$ | 2.6% | 3.6% | 3.4% | 0.9% |
| Hb<12 g/dL | 64% | 70.0% | 69.5% | 49.1%** |
| Platelet<50,000/ $mm^3$ | 3.5% | 2.7% | 1.7% | 0.9% |

*p-value<0.05 HSA-IFNα2b 1200μg Q2w vs. Q4w; [¶] p-value 0.068 HSA-IFNα2b 1200 μg Q2w vs. PEG-IFN; [#] p-value <0.05 HSA-IFNA2B 1200μg Q4w vs. PEG-IFN; **p-value <0.05 HSA-IFNα2b 1200μg Q4w vs. all other groups

**Table 11.** *Final Interim Analysis Demographic, Anti-viral Response, and Hematological Effect*

| | PEG-IFN 180 μg Q1w (n=114) | HSA-IFNα2b 1200 μg Q2w (n=110) | HSA-IFNα2b 900 μg Q2w (n=118) | HSA-IFNα2b 1200 μg Q4w (n=116) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Demographics** | | | | |
| Male | 58% | 58% | 56% | 67% |
| Mean BMI (kg/m$^2$) | 25.1 | 25.7 | 25.6 | 26.0 |
| • BMI ≥25 kg/m$^2$ | 50% | 48% | 51% | 50% |
| Median HCV RNA (log IU/ml) | 6.1 | 6.0 | 6.1 | 6.1 |
| • RNA ≥800,000 IU/ml | 62% | 55% | 56% | 62% |
| **Efficacy at Week 12 ITT** | | | | |
| HCV RNA Negative (<LOQ) | 75/114 (65.8%)[¶] | 82/110 (74.5%)[¶] | 82/118 (69.5%) | 62/116 (53.4%)* |
| • BMI <25 kg/m$^2$ vs. ≥25 kg/m$^2$ | 71.9% vs. 59.6% | 77.2% vs. 71.7% | 74.1% vs. 65.0% | 56.9% vs. 50.0% |
| EVR12 (≥2 log reduction) | 101/114 (88.6%) | 99/110 (90.0%) | 99/118 (83.9%) | 88/116 (75.9%) |
| 2$^{nd}$ phase slope >0.6 log/wk | 49% | 58% | 52% | 42% |
| Normalization of ALT | 11/73 (15.1%) | 17/79 (21.5%) | 17/80 (21.3%) | 26/83 (31.3%)[#] |
| **Efficacy at Week 20 ITT** | | | | |
| HCV RNA <LOD (undetectable) | 77/114 (67.5%) | 82/110 (74.5%) | 83/118 (70.3%) | 70/116 (60.3%) |
| **Efficacy at Week 24 MITT** | | | | |
| HCV RNA <LOD (undetectable) | 57/90 (63.3%) | 64/91 (70.3%) | 58/87 (66.7%) | 58/83 (69.9%) |
| **Laboratory at Week 12** | | | | |
| ANC<750/mm$^3$ | 20.2% | 21.8% | 22.0% | 6.0%** |
| ANC<500/ mm$^3$ | 3.5% | 3.6% | 3.4% | 1.7% |
| Hb<12 g/dL | 65% | 74% | 70% | 52%** |
| Platelet<50,000/ mm$^3$ | 3.5% | 2.7% | 1.7% | 0.9% |

*p-value<0.05 HSA-IFNα2b 1200μg Q2w vs. Q4w; [¶] p-value 0.15 HSA-IFNα2b 1200 μg Q2w vs. PEG-IFN; [#] p-value <0.05 HSA-IFNA2B 1200μg Q4w vs. PEG-IFN; **p-value <0.05 HSA-IFNα2b 1200μg Q4w vs. all other groups

*Antiviral Response Predictors of SVR*

**[1342]** An antiviral response predictor of SVR was defined as a negative HCV RNA titer (i.e., having an HCV RNA titer <LOQ) at week 12 of treatment with a second phase slope > 0.6 log/wk (2$^{nd}$ slope). The phases of the antiviral response curve slope are indicative of two activities. The first phase shows the direct antiviral activity of the response. The second phase predicts the destruction of the HCV infected cells by the treated compound. Thus a value of the second phase slope at > 0.6 log/wk is a good predictor of SVR (positive predictive value (PPV) >

90%).

**[1343]** Antiviral response predictors of SVR at week 12 ITT were greatest in the HSA-IFNα2b 1200 μg Q2w treatment group where 82/110 subjects or 74.5% ((final interim analysis) (77/104 or 74.0% (preliminary analysis))) had HCV RNA negative levels (i.e., levels below the LOQ (<43 IU/mL)) and 58% exhibited a second phase slope > 0.6 log/wk, as compared to 75/114 subjects or 65.8% ((final interim analysis) (70/112 or 62.5% (preliminary interim analysis))) and 49% in the PEG-IFN control treatment. These data indicate that the HSA-IFNα2b 1200 μg Q2w treatment protocol has antiviral activity that is at least comparable to conventional treatment with PEG-IFN at week 12. Because RNA negativity (i.e., the number of patients having HCV RNA titer levels below the LOQ) at week 12 in the HSA-IFNα2b 1200 μg Q2w treatment protocol is approximately 9% (final interim analysis) and 12% greater (preliminary interim analysis) and the second phase slope is approximately 9% greater (for both the final and preliminary interim analysis) compared to the PEG-IFN control treatment, it is likely that the HSA-IFNα2b 1200 μg Q2w treatment protocol may result in superior efficacy over the conventional PEG-IFN treatment. The number of patients having HCV RNA negativity in the HSA-IFNα2b 900 μg Q2w and HSA-IFNα2b 1200 μg Q4w treatment groups were similar to conventional treatment with PEG-IFN.

**[1344]** Antiviral response predictors of SVR at weeks 20 and 24 are indicated as subjects having HCV RNA titers below the level of detection (LOD) (i.e., <10 IU/mL). Antiviral response predictors of SVR at week 20 was greatest in the HSA-IFNα2b 1200 μg Q2w treatment group, where 82/110 subjects or 74.5% (final interim analysis) had undetectable HCV RNA levels (i.e., <10 IU/mL) as compared to 77/114 or 67.5% (final interim analysis) in the PEG-IFN control treatment. Similarly, antiviral response predictors of SVR at week 24 was greatest in the IFNα2b 1200 μg Q2w treatment group where 64/91 or 70.3% (final interim analysis) had undetectable HCV RNA levels whereas the PEG-IFN control treatment had 57/90 or 63.3% with undetectable HCV RNA levels. Both the week 20 and 24 data indicate that the HSA-IFNα2b 1200 μg Q2w treatment protocol has antiviral activity and safety that is at least comparable to conventional treatment with PEG-IFN with an improved dosing schedule.

*Normalization of ALT Levels*

**[1345]** A common measurement of liver function in a patient is the level of alanine transferase (ALT). One of the hallmarks of HCV infected patients is high serum ALT levels that are indicative of liver damage. Thus, the normalization of ALT levels corresponds with improvement in liver function and has a favorable prognosis for responding to treatment.

Although all treatment protocols exhibited some ability to normalize ALT levels, the most dramatic effect was observed in the HSA-IFNα2b 1200 μg Q4w treatment protocol, where over twice as many patients (final and preliminary interim analysis) achieved normalized ALT levels as compared to conventional treatment with PEG-IFN. Thus, HSA-IFNα2b dosed at 1200 μg Q4w is surprisingly more effective than conventional PEG-IFN treatment in normalizing liver function in genotype 1, IFN-naïve HCV patients.

*Hematological Effects*

**[1346]** Ensuring compliance and exposure to full doses of IFN and RBV in combination treatment protocols is critical for maximizing SVR rates.

**[1347]** Hematological reductions are common during combination treatment with IFN and RBV. Reductions in hemoglobin (Hb) due to RBV-induced hemolysis require dose reduction in RBV. In particular, Hb <12g/dL requires reducing RBV from 1000-1200 mg/day to 800 mg/day. RBV dose is critical to prevent HCV relapse. The HSA-IFNα2b 1200 μg Q4W treatment protocol surprisingly had significantly fewer reductions in Hb <12g/dL (52% vs. 65% for PEG-IFN (final interim analysis); 49.1 vs. 64% for PEG-IFN (preliminary interim analysis)). This may translate to a lower relapse rate with the HSA-IFNα2b 1200 μg Q4W treatment protocol, allowing for improved SVR.

**[1348]** Reductions in ANC <750/mm$^3$ requires dose reducing the IFN component of the combination treatment. Surprisingly, the HSA-IFNα2b 1200 μg Q4W treatment protocol had significantly fewer ANC <750/mm$^3$ compared to PEG-IFN (6% vs. 20.2%, respectively (final interim analysis); 4.3% vs. 17.5%(preliminary interim analysis)). This again may translate to higher SVE rates given the fewer dose reductions required with the HSA-IFNα2b 1200 μg Q4W treatment protocol.

**[1349]** Similar hematological reductions occurred across the HSA-IFNα2b Q2w and PEG-IFN treatment groups at week 12. Surprisingly, however, the hematological reductions observed in the HSA-IFNα2b 1200 μg Q4w treatment group at week 12 were approximately 75% lower than those observed in the PEG-IFN treatment group. These results indicate that HSA-IFNα2b Q4w may offer a superior safety profile and improved relapse rate as compared to conventional PEG-IFN treatment.

*Conclusion*

**[1350]** At week 12, the maximal antiviral activity in genotype 1, IFN-naïve HCV was observed in the HSA-IFNα2b 1200 μg Q2w treatment group. Similar effects on hematological reductions were also observed in the HSA-IFNα2b 1200 μg Q2w and PEG-IFN treatment groups.

Moreover, at weeks 20 and 24, the maximal antiviral activity was also observed in the HSA-IFNα2b 1200 μg Q2w treatment group. Comparable antiviral activity was continued to be observed at weeks 20 and 24 in the HSA-IFNα2b 900 μg Q2w treatment group. Accordingly, HSA-IFNα2b 900 μg Q2w may offer at least a comparable efficacy and safety profile to the current standard of care, PEG-IFN, with an improved dosing schedule, translating into a greater convenience for the patient. Additionally, 1200 μg Q2w may offer at least a comparable safety profile to the current standard of care, PEG-IFN, with a possible superior efficacy and an improved dosing schedule, translating into a greater convenience for the patient.

**[1351]** Treatment with the HSA-IFNα2b 1200 μg Q4w protocol surprisingly showed comparable efficacy at week 12 compared to the conventional PEG-IFN treatment even though subjects receiving the PEG-IFN conventional treatment received three additional doses due to the dosing schedule. Comparable efficacy of the HSA-IFNα2b 1200 μg Q4w compared to the conventional PEG-IFN treatment continued through weeks 20 and 24. Improved ability to stabilize liver function and dramatically reduce the reduction in hematological factors was also observed with HSA-IFNα2b 1200 μg Q4w treatment group at week 12, indicating an improvement in liver injury and a reduction in incidence of dose-reduction or temporary termination, and possibly relapse following treatment, in these patients. Thus, these results suggest that the treatment with HSA-IFNα2b 1200 μg Q4w may offer efficacy comparable to combination treatment with PEG-IFN with the advantage of an improved dosing schedule, a greater ability to normalize liver function, and lower hematological reductions, resulting in greater compliance and convenience for the patient, and more favorable outcome post-therapy. In summary, given recent advances in the field of HCV therapeutics, an HSA-IFNα2b Q4W treatment protocol would have the ideal attributes (e.g., comparable efficacy, superior tolerability, superior convenience resulting in greater compliance) to become the interferon-backbone-of-choice for an interferon-antiviral combination therapy.

**[1352]** Taken together, these results suggest that combination treatment of genotype 1, IFN-naïve HCV patients with HSA- IFNα2b and RBV is at least as effective as treatment with the conventional PEG-IFN and RBV combination treatment with the advantage of an improved dosing schedule. Particularly, these results suggest that treatment with HSA-IFNα2b in combination with RBV can have either an superior efficacy with a similar safety profile, a similar efficacy with an superior safety profile, or both a superior efficacy and safety profile compared to conventional PEG-IFN combination treatment with RBV, but with an improved and highly advantageous dosing schedule.

***Example 83: Response of Chronic Hepatitis C (HCV) Non-Responder Patients to HSA-IFNα2b, in Combination with Ribavirin***

*Background*

**[1353]** Over four million people in the United States have been infected with the hepatitis C virus (HCV), making the virus the most common cause of liver disease in the United States. Interferon alpha (IFNα) with or without concurrent treatment of the antiviral molecule, ribavirin (RBV), has historically been recognized as the most effective treatment for patients. More recently, pegylated forms of interferon alpha have been approved for treatment of HCV in combination with RBV. These peglyated interferons have been shown to be more effective in treating HCV than the standard interferon or interferon in combination with ribavirin therapies and have become the conventional treatment for HCV.

**[1354]** However, this treatment has significant practical limitations. In addition to the well-known side effects that substantially decrease a patient's quality of life during therapy and the considerable rate of significant hematological reductions associated with the conventional therapy, the conventional therapy is ineffective for a large proportion of the patients who undergo the current treatment for HCV. Clinical studies of treatment of HCV patients who have not previously received an IFNα-RBV therapy have shown that approximately 45% of patients who commence the conventional treatment fail to clear HCV and remain chronically infected (e.g., non-responders). In the community, the proportion of patients responding to therapy is considerably less.

**[1355]** Clinical investigators have responded to the need of the non-responder population of HCV patients who had failed to respond to a previous treatment with IFNα or in combination with RBV by retreating these patients with the conventional therapy of pegylated IFNα and RBV. *See*, Shiffman *et al.*, "Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment," *Gastroenterology* 126(4):1015-23 (2004). Although 35% of patients enrolled in this trial had no evidence of HCV RNA after 20 weeks of retreatment with the conventional therapy, many of these patients relapsed after treatment was discontinued. Thus, only 18% of the patients actually achieved a sustained viral response (SVR) and were cured of HCV. Similarly, when non-responder patients who had failed a previous treatment with conventional pegylated IFNα therapy were retreated with another pegylated IFNα, only ~5-10% of these patients were able to achieve SVR based on anecdotal evidence. Thus, the population of patients who have not only failed one interferon therapy but have failed all current interferon therapies continues to significantly grow. Accordingly, there is a clear need for improved

therapeutic protocols not only for the treatment of HCV in general but also for alternative therapies for treatment of those patients who have been previously treated with an interferon therapy (e.g., IFNα treatment-experienced) and who are non-responders, particularly those non-responder patients who are the most difficult to treat (e.g., patients who have failed previous treatment or retreatment with the current conventional care).

*Rationale*

**[1356]** HSA-IFNα2b was generated by genetically fusing mature albumin at its C-terminus to the N-terminus of mature interferon α-2b. The safety, tolerability, and efficacy of treatment with HSA-IFNα2b in combination with RBV was evaluated in randomized, open label clinical study in IFNα treatment-experienced, non-responder HCV human patients. For the purposes of this study, non-responders were defined as either those HCV patients who had stopped previous therapy at week 12 due a failure to achieve a 2-log reduction in HCV RNA levels (e.g., early viral response, week 12 or EVR12) or those patients who failed to achieve SVR after completion of the treatment protocol. Patients who relapsed after discontinuation of therapy were excluded from the study. In addition, at least 50% of the patients in the study previously failed a pegylated IFNα treatment protocol.

*Methods*

**[1357]** Human IFNα treatment-experienced, non-responder HCV patients who previously failed at least one IFNα treatment protocol were randomized into 3 subcutaneous (sc) HSA-IFNα2b treatment groups: (a) 900 μg once every 2 weeks (Q2w); (b) 1200 μg Q2w and (c) 1200 μg once every 4 weeks (Q4w). Each subject in each treatment group also received 1000-1200 mg/day RBV. After evaluation of safety data from these initial three cohorts, HSA-IFNα2b was dose escalated with the sequential addition of two additional cohorts who received HSA-IFNα2b at either 1500 μg Q2w or 1800 μg Q2w in combination with 1000-1200 mg/day RBV.

**[1358]** Treatment duration of the study is 48 weeks with a 24 week follow-up. The primary efficacy endpoint of the study is sustained virologic response (SVR).

**[1359]** HCV RNA titer was measured using a real-time PCR assay, Quantasure™ (Labcorp) with a sensitivity range of 10 IU to 100 million IU/mL). Alanine Transferase (ALT) and hematologic effects, including absolute neutrophil count (ANC), hemoglobin, and platelet count were measured using standard techniques known in the art.

*Results and Discussion*

*Demographics*

**[1360]** Numerous demographic characteristics have been identified that serve as independent

indicators of those patients who have a prevalence toward non-responding to treatment. These key pre-treatment predictors of non-responsiveness include (1) genotype 1, (2) high baseline median HCV RNA level, (3) prior non response to PEG+RBV therapy, (4) African-American, (5) an advanced Fibrosis level of F3-F4 (using the METAVIR® classification), and (6) high BMI (e.g., ≥ 25 mg/kg). Perhaps, the best overall indicator for non-responsiveness is previous failure of PEG-RBV treatment and in the context of the number of previous IFN based regimens failed.

**[1361]** Subject demographics are summarized in Table 12. Overall, all the subject demographics were similar in all the treatment groups. The majority of subjects had been exposed to more than one IFNα containing regimen and had failed previous therapy with PEG+RBV. In addition, while the baseline disease characteristics were comparable across the 5 treatment groups, the 1800 μg Q2w treatment group had a significantly higher pre-treatment HCV RNA and the highest proportion of prior PEG+RBV failures. Thus, the subjects in the 1800 μg Q2w treatment group represented the most treatment-refractory patient population.

**Table 12.** *Demographics and Baseline Characteristics*

| | **900 μg Q2w N=23** | **1200 μg Q2w N=24** | **1200 μg Q4w N=24** | **1500 μg Q2w N=22** | **1800 μg Q2w N=22** | **P value** |
|---|---|---|---|---|---|---|
| **Genotype 1** | 20 (87.0%) | 24 (100%) | 22 (91.7%) | 21 (95.5%) | 21 (95.5%) | 0.4531 |
| **Med HCV RNA ($log_{10}$IU/mL)** | 7.1 | 6.6 | 6.2 | 7.0 | 7.6 | < 0.0001 |
| **PEG+RBV** | 14 (60.9%) | 16 (66.7%) | 15 (62.5%) | 16 (72.2%) | 20 (90.9%) | 0.1370 |
| **African American** | 2 (8.7%) | 3 (12.5%) | 1 (4.2%) | 7 (31.8%) | 2 (9.1%) | 0.0940 |
| **F3 - F4** | 7 (30.4%) | 7 (29.2%) | 4 (16.7%) | 9 (40.9%) | 7 (31.8%) | 0.5012 |
| **BMI ≥ 25 kg/m2** | 20 (87.0%) | 21 (87.5%) | 18 (75.0%) | 18 (81.8%) | 17 (77.3%) | 0.7637 |

*Efficacy and Biological Activity*

**[1362]** Reductions in HCV RNA from pre-treatment levels over the treatment duration are shown in Table 13 for genotype 1, PEG+RBV nonresponders, the most refractory HCV patient population. At weeks 2-12, the magnitude of HCV RNA reduction was comparable across the 900-1500 μg treatment groups. However, the maximal viral load reductions were observed in the 1800 μg treatment group. This was surprising considering the higher levels of pre-treatment HCV RNA and the highest proportion of PEG+RBV failures in this treatment group. The

magnitude of antiviral response over the first 12 weeks of therapy reflects the second phase slope of viral kinetics and is a positive predictor of SVR.

**[1363]** As shown in Figure 12, the slopes of HCV RNA reduction are comparable at week 12 for the 900-1500 μg treatment groups in genotype 1, PEG+RBV nonresponders. Surprisingly, the magnitude of HCV RNA reduction is greatest for the 1800 μg treatment group. The HCV RNA reductions for the 1500 and 1800 μg treatment groups are comparable at week 24 in this sub-group of patients.

**[1364]** At week 24, the proportion of subjects who are HCV RNA negative was comparable across the 900-1500 μg treatment groups. Subjects were allowed to discontinue at week 24 for lack of efficacy at the discretion of the investigator and given the cumulative data from interferon-based regimens demonstrating the high negative predictive value of lack of EVR12 and week 24 RNA negativity for SVR. The overall end-of-treatment response (ETR, HCV negative at week 48) was 30% (22/73) for the 900-1200 μg treatment groups. Thus, a high proportion of subjects who became HCV RNA negative at week 12 (e.g., EVR12) or at week 24 achieved ETR. In addition, the majority of subjects (13/22) continued to be HCV RNA negative at the week 12 follow-up after 48 weeks of treatment. This indicates that the potential SVR following treatment with HSA-IFNα2b/RBV is 18%.

**[1365]** In summary, these data indicate that treatment of IFNα treatment-experienced, non-responder HCV patients, with a high percentage of PEG+RBV failures with 900-1200 μg of HSA-IFNα2b in combination with RBV results in robust and comparable antiviral activity. A low viral breakthrough (e.g., HCV RNA undetectable but subsequently positive at two or more time points) and relapse rate was also observed in this treatment refractory non-responder population. In addition, a significantly greater reduction was also observed in the 1800 μg treatment group over the first 12 weeks of therapy, indicating that patients treated at this dose with HSA-IFNα2b in combination with ribavirin may have a significant increase in SVR rates.

**Table 13** *Antiviral Response for GT1 and PEG+RBV Non-responders*

| | **900 μg Q2w N=12** | **1200 μg Q2w N=16** | **1200 μg Q4w N=13** | **1500 μg Q2w N=15** | **1800 μg Q2w N=19** |
|---|---|---|---|---|---|
| **Week 12 EVR12**[a] | 5 (41.7%) | 4 (25%) | 3 (23.1%) | 5 (33.3) | 12 (63.2%) |
| **95% C.I.**[b] | (15.1%, 72.3%) | (7.3%, 52.4%) | (7.2%, 52.4%) | (11.8%,61.6 %) | (38.4%,83.7 %) |

| | | | | | |
|---|---|---|---|---|---|
| **Week 24 Undetectable HCV RNA** | 2 (16.7%) | 3 (18.8%) | 2 (15.4%) | 4 (26.7%) | 6 (31.6%) |
| **95% C.I.**[b] | (2.1%, 48.4%) | (4.0%, 45.6%) | (1.9%, 45.4%) | (7.8%, 55.1%) | (12.6%, 56.6%) |
| **Week 48 ETR**[a] | 3 (25%) | 3 (18.8%) | 2 (15.4%) | | |
| **95% C.I.**[b] | (5.5%, 57.2%) | (4.0%, 45.6%) | (1.9%, 45.4%) | | |

[a]Defined as undetectable HCV RNA or a ≥ 2-log reduction in HCV RNA
[b]Exact 95% confidence interval.

*Hematological Effects*

**[1366]** Ensuring compliance and exposure to full doses of IFN and RBV in combination treatment protocols is critical for maximizing SVR rates.

**[1367]** Hematological reductions are common during combination treatment with IFN and RBV. RBV dose is critical to prevent HCV relapse. However, reductions in hemoglobin (Hb) and platelet (PLT) count due to RBV-induced hemolysis require dose reduction in RBV. Reductions in absolute neutrophil count (ANC) <750/mm$^3$ requires dose reducing the IFN component of the combination treatment.

**[1368]** Although some ANC and PLT reductions were observed, these reductions were comparable across all Q2w treatment groups and reached a plateau around weeks 4 to 8. Likewise, the Hb reductions from baseline were comparable across all the Q2w treatment groups (including the 1800 μg treatment group) until week 12 and beyond. Reductions in hematologic values were less in the Q4w treatment group. Overall, there were 12/115 subjects who were dose reduced for the management of adverse events. Most dose reductions of HSA-IFNα2b resulted from reductions in ANC as outlined in the treatment protocol. There was no dose response observed between the Q2w treatment groups. Thus, there was no increased need for dose reduction observed in the higher dose treatment groups.

**[1369]** In summary, although there were some reductions in hematologic values observed with treatment of HSA-IFNα2b in combination with RBV, these reductions were comparable across the treatment groups, indicating that there was no significant difference in safety between treating IFNα treatment-experienced, non-responder HCV patients with 900-1800 μg of HSA-IFNα2b in combination with RBV.

*Conclusion*

**[1370]** Taken together, these results suggest that treatment with HSA- IFNα2b and RBV may be

effective in achieving SVR, and thus eradicating HCV, in a significant portion of IFNα treatment-experienced, non-responder HCV patients, including those patients who previously failed a PEG+RBV treatment protocol. Particularly, these results suggest that treatment with HSA-IFNα2b 900-1200 μg in combination with RBV may result in 18% of patients achieving SVR, even after previously failing PEG+RBV. Moreover, the 1800 μg treatment group showed the greatest week 24 HCV RNA negativity rates in the most refractory patient population, indicating that this treatment may result in an even greater SVR rate for these patients. In addition, the safety profile was similar across all of the treatment groups of HSA-IFNα2b. Moreover, these results indicate that HSA-IFNα2b may be efficaciously administered every two to four weeks, providing an improved dosing schedule. Thus, these results indicate that the treatment of HSA-IFNα2b in combination with RBV provides an efficacious and safe treatment alternative with a high advantageous and improved dosing schedule, for those patients who fail an interferon-based therapy, particularly those that have failed the conventional pegylated interferon-RBV therapy that is currently lacking in the art.

***Example 84. Anti-Viral Activity of HSA-IFNα2b, in Combination with Ribavirin in Genotype 2 or 3, Interferon-Naïve Chronic Hepatitis C (HCV) Patients***

*Background*

**[1371]** With more than 170 million people infected with the Hepatitis C virus (HCV) worldwide, this virus has emerged as a significant public health concern and has rapidly become the most common cause of liver disease throughout the world. Acute HCV infection is usually asymptomatic, making early diagnosis problematic. In fact, HCV infection tends to be a chronic condition, where approximately 70% of acute infections becoming persistent. Thus, although the incidence of new infections has been on the decline, the prevalence of HCV infection is predicted to remain constant in the near future.

**[1372]** Interferon alpha (IFNα) with or without concurrent treatment of an antiviral molecule, ribavirin (RBV), has historically been recognized as the most effective treatment for patients with chronic hepatitis C (CHC). More recently, pegylated forms of interferon alpha have been approved for treatment of HCV in combination with RBV. These peglyated interferons have been shown to be more effective in treating HCV than the standard interferon or interferon in combination with ribavirin therapies and have become the conventional treatment for HCV.

**[1373]** Overall sustained anti-viral responses (SVR) to the currently recommended therapy vary greatly in CHC patients, depending on viral and host characteristics, particularly viral genotype. For example, SVR rates range from approximately 42-46% in patients with the more common

genotype 1. On the other hand, patients with the less common genotypes 2 or 3 experience SVR rates at 76-80%. In addition, genotype 2 or 3 patients, who are considerably less difficult to treat than genotype 1 patients can be treated for a shorter duration of therapy with a lower dose of ribavirin.

**[1374]** Although the currently recommended therapy for genotype 2 or 3 of pegylated interferon in combination with RBV for 24 weeks followed by a 24 week follow-up period results in a significant proportion of patients achieving SVR, this treatment protocol still retains significant practical limitations common to IFN-based therapies. In particular, the currently recommended therapy remains plagued by adverse effects that substantially decrease the patient's quality of life after each administration. Thus, there is a continued need for new treatment regimens that are efficacious and better tolerated by patients infected with genotype 2 or 3 HCV.

*Rationale*

**[1375]** HSA-IFNα2b was generated by genetically fusing mature albumin at its C-terminus to the N-terminus of mature interferon α-2b. The safety and efficacy of treatment with HSA-IFNα2b in combination with RBV was evaluated in a randomized, multi-center, open-label clinical study in genotype 2 or 3, IFN-naïve CHC human patients.

*Methods*

**[1376]** 43 human HCV patients who were either genotype 2 or 3, IFN-naive were randomized into two subcutaneous (sc) HSA-IFNα2b treatment groups: (a) 1500 μg dosed every two weeks (Q2w) or (2) 1500 μg dosed every four weeks (Q4w). Each subject in each treatment group also received in 800 mg/day of RBV. The primary basis for stratification included genotype (2 or 3) and HCV RNA (<800,000 IU/mL or ≥ 800,000 IU/mL).

**[1377]** Treatment duration of the study is 24 weeks with a 24 week follow-up. The primary efficacy end-point is sustained virologic response (SVR).

**[1378]** HCV RNA titer was measured using real-time PCR, Quantasure™ (Labcorp) with a sensitivity range (limit of quantitation (LOQ)) of 43 IU to 69 million IU/mL. Insulin resistance was assessed using Homeostasis Assessment Model (HOMA).

**[1379]** Intent to treat (ITT) patients are defined as all randomized and treated subjects of each treatment group, regardless of whether or not the patient has any missing data points or has dropped out of the study. Modified intent to treat (MITT) patients are defined as those patients that could conceivably have a Week 12 visit based on their date of enrollment in the study.

*Results and Discussion*

**[1380]** Subject demographics and antiviral response at weeks 4 and 12 are summarized in Table

14. Overall, HSA-IFNα2b was well-tolerated in both treatment groups.

**Table 14.** *Demographics and Anti-Viral Response.*

| | HSA-IFNα2b 1500 µg Q2w (N=21) | HSA-IFNα2b 1500 µg Q4w (N=22) |
|---|---|---|
| **Demographics** | | |
| **% male** | 71.4% | 68.2% |
| **% HCV RNA ≥800,000** | 71.4% | 59.1% |
| **Mean HOMA pre-treatment** | 2.2 | 2.5 |
| **Week 4 (<LOQ) ITT** | 16/21 (76.2%) | 15/22 (68.2%) |
| **Genotype 2** | 8/10 | 6/10 |
| **Genotype 3** | 8/11 | 9/12 |
| **Week 12 (<LOQ) MITT** | 14/17 (82.4%) | 16/18 (88.9%) |
| **Genotype 2** | 7/9 | 9/9 |
| **Genotype 3** | 7/8 | 7/9 |

ITT= intent to treat; MITT= modified intent to treat (subjects eligible for week 12 visit)

**[1381]** The magnitude of HCV RNA reduction and the proportion of genotype 2 or 3 patients with HCV RNA< LOQ were comparable across both the HSA-IFNα2b Q2w and HSA-IFNα2b Q4w treatment groups. At week 4, the proportion of genotype 2 or 3 patients with HCV RNA< LOQ was 76.2% in the 1500 µg Q2w and 68.2% in the 1500 µg Q4w treatment group. At week 12, a high proportion of genotype 2 or 3 patients in both treatment groups had HCV RNA< LOQ (82.4% in the 1500Q2w and 88.9% in the 1500Q4w).

**[1382]** Thus, these results indicate that the treatment of genotype 2 or 3 CHC patients with 1500 µg HSA-IFNα2b at either Q2w or Q4w weeks results in a robust antiviral response rate. Moreover, treatment with the HSA-IFNα2b 1500 µg Q4w protocol showed comparable efficacy to treatment with the HSA-IFNα2b 1500 µg Q2w protocol in genotype 2 or 3 patients. Thus, these results suggest that the treatment with HSA-IFNα2b 1500 µg at either Q2w or Q4w is at least as effective as the currently recommended therapy for patients infected with HCV genotype 2 or 3 with the advantage of a vastly improved dosing schedule, potentially resulting in superior tolerability and convenience for the patient.

***Example 85. Quality of Life (QOL) of Genotype 1, Interferon-Naïve Chronic Hepatitis C (HCV) Patients Treated with HSA-IFNα2b, in Combination with Ribavirin Patients***

*Background*

**[1383]** As previously noted, the conventional treatment for genotype 1, interferon-naïve (IFN-naïve) HCV patients with pegylated interferon α in combination with ribavirin (RBV) for 48 weeks has significant practical limitations. Due to the well-known side effects of currently recommended interferon therapy, patients' quality of life is substantially decreased after each

administration of interferon. Current protocols require dosing at least weekly, resulting in a prolonged period of decreased quality of life and increase in disability days due to treatment. Large numbers of patients discontinue treatment as a result, with some studies reporting discontinuation rates over 50%. Thus, there is an clear need for improved therapeutic protocols for the treatment of genotype 1 HCV in IFN-naïve patients with improved impact on quality of life compared to the current standard of care.

*Rationale*

**[1384]** The safety and efficacy of treatment with HSA-IFNα2b in combination with RBV was evaluated in an active controlled clinical study in genotype 1, IFN-naïve HCV human patients, and compared to conventional treatment with PEG-IFNα-2a (PEG-IFN) in combination with RBV as an active control as described in Example 82. During the first twelve weeks of therapy, the effects on QOL and disability days (e.g., days missed from work) of treatment with treatment with HSA-IFNα2b in combination with RBV were compared with PEG-IFN in combination with RBV.

*Methods*

**[1385]** 458 human, genotype 1 HCV patients were randomized and treated as described in Example 82. QOL as determined by the SF-36v2® measurement model (QualityMetric, Lincoln, RI) and disability days were assessed pre-treatment, and at week 4 and week 12 of treatment. In particular, eight SF-36v2 domains were assessed: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The first four domains (PF, RP, BP, and GH) correspond to the Physical Health Component and the remaining four domains (VT, SF, RE, and MH) correspond to the Mental Health Component of the QOL model.

**[1386]** Transformed (raw) scores of the eight SF-36v2 domains, as well as norm-based physical component summary (PCS) score and mental component summary (MCS) score were evaluated through week 12 of treatment.

*Results and Discussion*

**Table 15.** *Quality of Life Measurements*

| | **PEG-IFN 180μg Qw (n=114)** | **HSA-IFNα2b 900μg Q2w (n=118)** | **HSA-IFNα2b 1200μg Q2w (n=110)** | **HSA-IFNα2b 1200μg Q4w (n=116)** |
|---|---|---|---|---|
| **SF-36 Domain (MCID)** | Mean change (worsening) from baseline to Week 12 in SF-36 QOL parameters | | | |
| PCS (2.6) | -8.0 | -5.6* | -6.5 | -6.0 |
| Physical Functioning (5) | -18 | -14 | -16 | -13 |
| Bodily Pain (4) | -21 | -11*# | -14# | -15# |

| | | | | |
|---|---|---|---|---|
| MCS (2.7) | -6.3 | -3.6*# | -4.9 | -5.0 |
| Vitality (4.2) | -19 | -13*# | -17 | -16 |
| Mental Health (4) | -11 | -4*# | -7# | -4*# |
| Social Functioning (6) | -20 | -10*# | -15 | -19 |
| **Missed work at Week 4** | Number of days missed in the prior month among subjects working for pay at the time of assessment | | | |
| Mean days missed | 4 | 1* | 3 | 3 |
| ≥ 3 days | 21/63 (33%) | 5/66 (8%)* | 17/61 (28%) | 15/62 (24%) |
| ≥ 7 days | 14/63 (22%) | 3/66 (5%)* | 8/61 (13%) | 7/62 (11%) |
| **Missed work at Week 12** | | | | |
| Mean days missed | 4 | 1* | 3 | 3 |
| ≥ 3 days | 21/69 (30%) | 7/70 (10%)* | 13/59 (22%) | 17/72 (24%) |
| ≥ 7 days | 12/69 (17%) | 3/70 (4%)* | 7/59 (12%) | 8/72 (11%) |

*p-value<0.05 vs. Peg-IFN; #exceeds (MCID) minimal clinically important difference

**[1387]** At week 12, QOL for patients receiving 900 μg HSA-IFNα2b Q2w was improved relative to PEG-IFN for every measure, achieving statistical significance in MCS and PCS, as well as 5 of the 8 individual domains. In the 1200 μg Q2w and 1200 μg Q4w HSA-IFNα2b treatment groups, worsening of QOL was reduced relative to PEG-IFN in virtually every measure, with clinically significant differences observed in both bodily pain and mental health.

**[1388]** Overall, genotype 1 HCV patients in any of the HSA-IFNα2b treatment groups missed fewer days of work (MDW) due to their HCV infection and subsequent therapy than genotype 1 HCV patients in the PEG-IFN treatment group. In particular, patients receiving 900 μg HSA-IFNα2b Q2w had 75% fewer MDW and patients receiving 1200 μg HSA-IFNα2b Q2w or 1200 μg HSA-IFNα2b Q4w had 25% fewer MDW than patients receiving PEG-IFN.

**[1389]** Taken together with the antiviral activity of HSA-IFNα2b shown in Example 82, these results suggest that combination treatment of genotype 1, IFN-naïve HCV patients with HSA-IFNα2b and RBV is at least as effective as treatment with the conventional PEG-IFN and RBV combination treatment with the advantage of an improved dosing schedule and a improved QOL. Particularly, these results suggest that treatment with HSA-IFNα2b in combination with RBV can provide an improved and highly advantageous treatment protocol over the conventional PEG-IFN combination treatment with RBV by providing patients with a reduction in worsening of QOL indicia and fewer missed days of work over that obtainable with the PEG-IFN combination treatment with RBV.

***Example 86. In Vivo Induction of cGMP by HSA-BNP (Construct ID # 3959) in a***

***Normal Pig Model***

***Rationale***

**[1390]** The ability of Brain (B type) natriuretic peptide (BNP) to mediate cellular effects such as modification of renal function and vascular tone is well-known in the art. The activity of BNP is dependent upon its binding to and subsequent activation of natriuretic receptor A (NPR-A) which is a guanylyl cyclase. The activation of NPR-A by BNP leads to an elevation of intracellular cGMP levels that can be measured by assays known in the art, such as, for example, ELISA. The ability of HSA-BNP (CID 3959) to induce the production of cGMP in vivo was tested in a normal pig model.

***Methods***

**[1391]** HSA-BNP (CID 3959) was generated by genetically fusing mature albumin at its C-terminus to the N-terminus of a C-terminally truncated form of BNP (amino acids 1 to 29).

**[1392]** Normotensive, healthy pigs (n= 4-6/group) were administered a single bolus of 5 mg/kg HSA-BNP (CID 3959) or formulation vehicle alone at time 0. Plasma and urine were collected at 1, 8, 16, 24, 48, and 72 hours post injection. cGMP levels in the collected plasma and urine were measured by commercially available ELISA (Molecular Dynamics).

***Results***

**[1393]** Single IV bolus of 5 mg/kg HSA-BNP (CID 3959) resulted in a significant elevation of both plasma (Figure 13A) and urine (Figure 13B) cGMP levels at 1 hour after IV administration. cGMP levels declined gradually to baseline levels at 24 hours in the plasma and by 48-72 hours in the urine.

***Example 87. Natriuresis Activity of BNP-HSA Fusion Construct in a In Vivo Pacing Model of Heart Failure***

***Background***

**[1394]** Administration of exogenous BNP has been utilized to facilitate natriuresis in congestive heart failure (CHF). However, recent studies have suggested that BNP administration can adversely affect renal function. The effect on renal or left ventricular (LV) function of HSA-BNP (CID 3959) was assessed in an in vivo severe CHF pig model. Surprisingly, the results of this study demonstrate that unlike BNP administration, acute infusion of HSA-BNP (CID 3959) can induce natriuresis without adversely affecting left ventricular or renal function.

***Methods***

**[1395]** HSA-BNP (CID 3959) was generated by genetically fusing mature albumin at its C-terminus to the N-terminus of a C-terminally truncated form of BNP (amino acids 1 to 29).

[1396] CHF was induced in 18 pigs by chronic pacing at 240 bpm for 3 weeks. 8 pigs served as reference controls. The following baseline characteristics were significantly reduced with CHF compared to reference controls. Baseline measurements were taken using techniques known in the art.

**Table 16.** ***Baseline measurements in CHF-induced pigs vs. reference control pigs***

| | CHF-Induced Pigs | Control Pigs |
|---|---|---|
| **Left Ventricular Fractional Shortening by Echocardiography (LVFS) (%)** | 21 ± 2 | 32 ± 2 |
| **Renal Vascular Blood Flow using Microspheres (RenFlow) (mL/min/g)** | 1.73 ± 0.09 | 2.23 ± 0.26 |
| **Sodium Clearance ($Na_{CL}$) (mL/min)** | 0.43 ± 0.11 | 4.35 ± 2.45 |
| **Fractional Excretion of Sodium ($FE_{Na}$) (%)** | 0.25 ± 0.07 | 0.80 ± 0.32 |

[1397] Following baseline measurements, animals with evidence of heart failure (e.g., LV dilation occurred with a subsequent decline in fractional shortening) were randomized for this study. The animals were anesthetized (n=10/group), administered either vehicle, 2 mg/kg HSA-BNP (CID 3959) or 6 mg/kg HSA-BNP (CID 3959) IV and monitored for 4 hours. End diastolic diameter was measured by echocardiography.

***Results and Conclusions***

[1398] Neither dose of HSA-BNP (CID 3959) had a significant effect on heart rate, mean arterial blood pressure, left ventricular end diastolic pressure, mean pulmonary arterial pressure, left ventricular peak pressure, peak positive dp/dt or cardiac output (data not shown). No change in coronary blood flow was seen in animals infused with either dose of HSA-BNP (CID 3959) (data not shown). In addition, although infusing the animals with 6 mg/kg of HSA-BNP (CID 3959) resulted in increased creatinine clearance and fractional sodium excretion 30 minutes post-infusion, neither reached statistical significance over baseline (data not shown). Similarly, infusion of 6 mg/kg of HSA-BNP (CID 3959) resulted in a non-significant reduction in plasma renin activity and endothelin plasma levels compared to vehicle (data not shown).

[1399] Significant increases in sodium clearance (492 ± 281% at 30 minutes post-infusion and 950 ± 483% at 60 minutes post-infusion) over vehicle were seen in animals infused with 6 mg/kg HSA-BNP (CID 3959). Additionally, end-diastolic diameter changes caused by the pacing were significantly reduced after either dose of HSA-BNP (CID 3959) compared to vehicle (Figure 14A). Moreover, changes in left ventricular fractional shortening were caused by the pacing were reduced after either dose of HSA-BNP (CID 3959) compared to vehicle, with the reduction

caused by the 2 mg/kg dose of HSA-BNP (CID 3959) being significant over vehicle (Figure 14B).

**[1400]** Thus, taken together, these results demonstrate that acute infusion of HSA-BNP (CID 3959) can induce natriuresis without adversely affecting left ventricular or renal function in an in vivo CHF model.

***Example 88. Effect of HSA-BNP (Construct ID #3959) on Cardiorenal Function in Anesthetized Normal Dogs***

***Rationale***

**[1401]** The ability of Brain (B type) natriuretic peptide (BNP) to mediate modification of renal function and vascular tone is well-known in the art. A particularly useful model for studying the effects of BNP on cardiorenal function is the dog. Accordingly, an extensive assessment of cardiorenal effects, including hemodynamic, renal, and hormonal effects, of HSA-BNP (CID 3959) was performed in an anesthetized normal dog model.

***Methods***

**[1402]** HSA-BNP (CID 3959) was generated by genetically fusing mature albumin at its C-terminus to the N-terminus of a C-terminally truncated form of BNP (amino acids 1 to 29).

**[1403]** Hemodynamic, renal, and hormonal parameters of cardiorenal function were evaluated in this study. In particular, the hemodynamic parameters included measurement of cardiac output, mean arterial pressure, pulmonary capillary wedge pressure, and mean pulmonary artery pressure. Renal parameters included measurement of urine flow, sodium excretion, glomerular filtration rate (GFR), and renal blood flow. Hormonal parameters included measurement of plasma cGMP, renin, angiotensin II, aldosterone, and urinary cGMP.

**[1404]** Normal healthy mongrels (n=8/group) were fed a fixed sodium diet for 5 days prior to the start of the study. On the night before the acute experiment, the animals were fasted and given 300 mg of lithium carbonate for assessment of renal tubular function. On the day of the acute experiment, the dogs were anesthetized via IV with sodium pentobarbital (15 mg/kg), intubated, and mechanically ventilated with supplemental oxygen.

**[1405]** A flow-directed balloon-tipped thermodilution catheter was advanced into the pulmonary artery via the external jugular vein for cardiac hemodynamic measurement. The femoral artery was cannulated for blood pressure monitoring, blood sampling, and for inulin and normal saline infusion. The ureter of the left kidney was cannulated for urine collection. A calibrated electromagnetic flow probe was placed around the renal artery to measure renal blood flow (RBF).

[1406] On the day of the acute experiments, the dogs were administered a single IV bolus of HSA-BNP (CID 3959) at either 0.5 mg/kg or 5 mg/kg (n= 8/group). Effects on cardiorenal function were monitored for 4.5 hours.

[1407] Cardiovascular parameters measured included mean arterial pressure (MAP), renal artery pressure (RAP), pulmonary artery pressure (PAP), cardiac output (CO), and pulmonary capillary wedge pressure (PCWP). CO was determined by thermodilution. MAP was assessed via direct measurement from the femoral arterial catheter. GFR was measured by inulin clearance.

[1408] Cardiovascular hemodynamics were measured at the start of each clearance. Arterial blood was collected in heparin and EDTA tubes and immediately placed on ice midway through each clearance. After centrifugation at 2,500 rpm at 4°C, plasma was decanted and stored at -20°C until analysis. Urine was collected on ice during the entire period of each clearance for assessment of urine volume, electrolytes and inulin. Urine collected for cGMP analysis was heated to more than 90°C before storage.

***Results and Discussion***

[1409] ***Hemodynamic Effects***

[1410] Figures 15A-H show the effect of HSA-BNP (CID 3959) administered at 0.5 mg/kg (Figures 15A, C, E, and G) or 5 mg/kg (Figures 15B, D, F, and H) on hemodynamic performance over 4.5 hours post-infusion compared with baseline readings. Hemodynamic parameters were measure at baseline prior to the IV bolus of HSA-BNP (CID 3959) and at 30, 60, 90, 150, 210, and 270 minutes post-infusion.

[1411] The hemodynamic effects of HSA-BNP (CID 3959) were sustained over the 4.5 hr observation period. Both 0.5 and 5 mg/kg IV bolus of HSA-BNP (CID 3959) resulted in a statistically significant and sustained reduction in pulmonary capillary wedge pressure (PCWP) (Figures 15E and F). The magnitude of reduction in PCWP with these two doses was not significantly different.

[1412] Effects of HSA-BNP (CID 3959) were dose-related for pulmonary arterial pressure (PAP) (Figures 15G and H) and mean arterial pressure (MAP) (Figures 15C and D). Significant reductions in PAP were observed when the animals were dosed at 5 mg/kg (Figure 15H). Likewise, a significant effect on MAP where observed at 270 minutes post-infusion in the 5 mg/kg treatment group (Figure 15D).

[1413] ***Renal Effects***

[1414] Figures 16A-H show the effect of HSA-BNP (CID 3959) administered at 0.5 mg/kg (Figures 16A, C, E, and G) or 5 mg/kg (Figures 16B, D, F, and H) on renal output and blood

flood over the 4.5 hours post-infusion compared with baseline readings. Renal performance parameters were measured at baseline prior to IV bolus of HSA-BNP (CID 3959) and at 30, 60, 90, 150, 210, and 270 minutes post-infusion.

**[1415]** Administration of HSA-BNP (CID 3959) resulted in significant effects on renal function. Significantly elevated renal blood flow (Figures 16E and F), diuresis (Figures 16A and B), natriuresis (Figures C and d) were observed at both 0.5 and 5 mg/kg HSA-BNP (CID 3959). A dose-related trend in increased GFR was also apparent (Figures 16G and H).

**[1416]** The time to maximal effect of HSA-BNP (CID 3959) on the renal parameters tended to be slightly delayed compared with the hemodynamic effects. In addition, the magnitude of the increase in natriuresis and diuresis was significantly higher in the 5 mg/kg treatment group than in the 0.5 mg/kg treatment group.

**[1417]** ***Hormonal Effects***

**[1418]** Figures 17A-F show the effect of HSA-BNP (CID 3959) administered at 0.5 mg/kg (Figures 17A, C, and E) or 5 mg/kg (Figures 17B, D, and F) on the RAAS hormones over 4.5 hours post-infusion compared with baseline readings. Plasma aldosterone, renin, and angiotensin II levels were measured at baseline prior to IV bolus of HSA-BNP (CID 3959) and at 30, 60, 90, 150, 210, and 270 minutes.

**[1419]** Administration with both 0.5 and 5 mg/kg IV bolus of HSA-BNP (CID 3959) resulted in a reduction of renin, angiotensin and aldosterone levels during the 4.5 hours post-infusion observation period. The effect on aldosterone levels was significant and sustained throughout the 270 minute study. Effects on renin and angiotensin II were significant between 30 and 90 minutes after administration of HSA-BNP (CID 3959) at both doses, but rebounded toward the end of the observation period.

***Conclusion***

**[1420]** This study demonstrates that HSA-BNP (CID 3959) behaves in a similar pharmacological manner as unfused BNP. Administration of HSA-BNP (CID 3959) in a single IV bolus at 0.5 and 5 mg/kg resulted in dose-dependent, significant, and sustained changes in multiple cardiorenal parameters that are consistent with its action as a long-acting form of BNP. In particular, administration of HSA-BNP (CID 3959) resulted in increased plasma and urine cGMP levels, reduced PCWP and PAP, increased natriuresis, diuresis, renal blood flow and glomerular filtration rate, decreased plasma, aldosterone, renin, and angiotensin II, and a slight reduction in MAP at the 5 mg/kg dose. Differential effect on component of the renin-angiotensin-adosterone system is somewhat unexpected result and may be a favorable attribute of HSA-BNP (CID 3959).

[1421] Taken as a whole, these results suggest that HSA-BNP (CID 3959) may administered at a dose that improves cardiorenal function without substantial unwanted reductions in systemic blood pressure.

***Example 89. Effect of HSA-BNP (Construct ID #3959) on Blood Pressure in Telemeterized Beagles***

***Rationale***

[1422] The ability of Brain (B type) natriuretic peptide (BNP) to mediate vascular tone is well-known in the art. As noted previously, a particularly useful model for studying the effects of BNP on cardiovascular function, including blood pressure, is the dog. Accordingly, the effect of intravenous (IV) administration of HSA-BNP (CID 3959) on cardiovascular function, including systolic and mean arterial blood pressure and heart rate was evaluated in conscious normal beagle dogs. Additionally, the effectiveness and duration of response of subcutaneous (SC) administration of HSA-BNP (CID 3959) was also evaluated.

***Methods***

[1423] Healthy beagles (n= 4/group) were surgically implanted with a Data Sciences International radiotelemetry transmitter, which had systemic arterial blood pressure, heart rate, and ECG data collection capabilities. Following implantation, the dogs received either a single IV bolus of 0.1, 0.5, or 5 mg/kg of HSA-BNP (CID 3959) or vehicle.

[1424] Continuous recording of ECG parameters and systemic blood pressure were monitored for 48 hours following infusion. The dogs were followed for an additional 9 days (total time = 11 days) with intermittent monitoring.

[1425] The effectiveness and duration of response of subcutaneous administration of HSA-BNP (CID 3959) on systemic blood pressure was evaluated by comparing the effect of administration of an IV bolus of unfused BNP (0.02 mg/kg) to administration of an SC administration of HSA-BNP (CID 3959) (10 mg/kg).

***Results and Discussion***

[1426] *Effect of HSA-BNP (CID 3959) on Systolic and Mean Arterial Blood Pressure*

[1427] Figures 18A-C show the effect of a single IV bolus of HSA-BNP (CID 3959) on the systolic and mean arterial blood pressure in awake dogs. Administration of 5 mg/kg HSA-BNP (CID 3959) resulted in gradual reductions in systolic blood pressure with a peak effect at approximately 16 hours and a return to baseline by 48 hours. A sustained reduction in systolic blood pressure of approximately 15 mmHg was apparent starting at 8 hours following drug administration and continuing through 20 hours following administration.

**[1428]** Administration of HSA-BNP (CID 3959) did not have any obvious effect on diastolic blood pressure or heart rate over the same observation period (data not shown).

**[1429]** Lower doses (e.g., 0.5 and 0.1 mg/kg) of HSA-BNP (CID 3959) were without obvious effect on either blood pressure or heart rate. In addition, there were no treatment-related changes on ECG parameters observed at any dose of HSA-BNP (CID 3959).

**[1430]** *Comparison of IV Administered Unfused BNP Peptide to SC Administered HSA-BNP (CID 3959)*

**[1431]** Figures 19A and B show the effect of an IV bolus of unfused BNP on systemic blood pressure in normal healthy beagles compared to a SC injection of HSA-BNP (CID 3959). Both HSA-BNP (CID 3959) and unfused BNP reduced systolic blood pressure in healthy beagles. The effect of unfused BNP was maximal at approximately 30 minutes and returned to baseline within hours. In contrast, the effect of HSA-BNP (CID 3959) was apparent approximately 10 hours after SC administration, reached a maximum at approximately 40 hours and returned to baseline between 48 and 72 hours post-injection. The slow onset effect of HSA-BNP (CID 3959) on blood pressure is consistent with its slow absorption (Tmax ~ 36 hours in the dog). The long duration of effect of HSA-BNP (CID 3959) is consistent with its long half life (72 hours in the dog).

**[1432]** Taken as a whole, these results suggest that HSA-BNP (CID 3959) may administered to heart failure patients at a dose low enough to improve cardiorenal function without having an effect on systemic blood pressure.

***Example 90. Use of BChE albumin fusions for cocaine breakdown and detoxification***

**[1433]** The purpose of this experiment was to determine the affect of an albumin BChE fusion on cocaine breakdown and detoxification.

***A. Construction and purification of BChE-albumin fusion: Albu-CocH***

**[1434]** A mutated, c-terminal-truncated form of human BChE (deleting the last 45 amino acids of the C-terminus, the tetramerization domain) was fused to the N-terminus of the mature form of HSA (gi:28592). **FIGURE 20** (termed "Albu-CocH" in this example). A signal peptide consensus sequence (amino acids 1-23 in **FIGURE 20**) was also fused to the N-terminus of the BChE portion of the fusion. The first amino acid in the mature BChE protein in the fusion corresponds to E29 of the unprocessed, full-length BChE protein. The mutations in the BChE portion of the fusion are as follows (the amino acid positions are relative to the unprocessed, full-length BChE): A227S, S315G, A356W, Y360G (bold, underlined amino acids in **FIGURE 20**).

The HSA portion of the fusion begins at amino acid 553 of **FIGURE 20.**

**[1435]** Monomeric protein was expressed in Chinese hamster ovary cells and purified to near homogeneity using blue affinity and ion exchange chromatography. Protein purity was assessed as greater than 95% based on N-terminal sequencing, high performance size-exclusion chromatography, and active-site titration.

## *B. Materials and Methods*

### *1. Animals*

**[1436]** Animals were handled according to the Principles of Laboratory Animal Care (National Research Council, 2003) in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care, under IACUC protocols A9306 (Mayo Clinic) and 0410A64760 (University of Minnesota). Wistar rats were obtained from Harlan Sprague-Dawley (Madison WI). Females (20 total, weighing approximately 225 at study onset) were used in behavioral experiments. Males (94, weighing 250-300g) were used for the other experiments.

**[1437]** On arrival at the behavior laboratory, rats were pair-housed in plastic cages and allowed to acclimate at least 3 days. Initially, all rats had free access to food (Purina Laboratory Chow, Purina Mills, Minneapolis, MN) and water. During the experiments they received 16 g of food at 3:00 pm daily, which held them to 85% of the weight of free-fed age-matched controls. Room lights were on from 6:00 am to 6:00 pm. Temperature (24°C) and humidity were kept within a narrow range. The rats for locomotor study remained pair-housed except for the testing procedures (activity at 9:00-9:30 am; food reinforcement at 1:00 pm-3:00 pm). For the reinstatement task rats were permanently transferred to operant chambers (see *Behavioral apparatus*).

### *2. Drug, reagents, and enzymes*

**[1438]** Drugs were prepared in 0.9% NaCl (saline). Cocaine HCl was from Mallinckrodt (St. Louis MO). Other drugs including atropine sulfate, ketamine, amphetamine sulfate, di-isopropylfluorophosphate (DFP), and sodium pentobarbital were from Sigma Aldrich (St. Louis). Each batch of enzyme was titrated by incubation for 24 hr with varying amounts of the irreversible inhibitor, DFP, followed by determination of residual activity (Sun et al., 2002a).

### *3. Radiometric assay of plasma and tissue samples*

**[1439]** Blood (100-300 µl) was collected from tail vein or femoral artery into heparin-treated

tubes and centrifuged (10 min at 8,000 g) to obtain plasma. Brains and hearts were homogenized in 10 volumes of 10 mM sodium phosphate, pH 7.4 with 0.5% Tween-20, and centrifuged as above. Cocaine hydrolase activity in 50 µl supernatant aliquots was assayed by incubating 30 min with $^{3}$H cocaine (18 µM, except for substrate kinetics) and measuring liberated $^{3}$H- benzoic acid (Brimijoin et al., (2002) *Analytical Biochemistry* **309**:200-205.).

**[1440]** To assess drug metabolism, pentobarbital-anesthetized rats (45 mg/kg, i.p.) received $^{3}$H-cocaine (3.5 mg/kg, 30 µCi, i.v.). At times from 30 sec to 2 hr, blood (≈ 150 µl) was collected from the femoral artery into tubes with DFP (10 µl, $10^{-2}$ M) added to inhibit BChE and carboxylesterase. Plasma samples were frozen on liquid nitrogen for assay later that day. Brains and hearts, frozen after aortic perfusion with 100 ml of isotonic NaCl plus DFP, $10^{-5}$ M, were later homogenized in phosphate-Tween buffer with the same inhibitor. Aliquots for determination of cocaine (acidified with 1 ml of 0.2 N HCl) or benzoic acid (alkalinized with 300 µl of 1M Na2CO3) were extracted directly into toluene for scintillation counting.

*4. Blood pressure recording*

**[1441]** For continuous monitoring of blood pressure, the rats were anesthetized with urethane (1.45 g/kg, i.p.). A sterile PE-50 cannula was then placed in one femoral artery and connected to a calibrated pressure transducer (Gould TA240). Body temperature was maintained by a heat lamp. Animals stabilized for 30 min before drug administration.

*5. Toxicity of cocaine overdose*

**[1442]** Rats were dosed with i.p. cocaine from 30 to 1000 mg/kg. Challenges with 100 mg/kg had been found regularly lethal in unprotected animals. Death was not an endpoint for the present studies, which instead used seizures as an index of serious toxicity. A battery of cage-side observations noted posture, gait, locomotor activity, paw licking, head bobbing, piloerection, and labored breathing. Onsets of convulsions were recorded. Rats were euthanized (sodium pentobarbital, 250 mg/kg i.p.) if they convulsed once for 60 sec or twice within 2 min.

*6. Behavioral Apparatus*

**[1443]** The operant chambers were custom octagonal units with alternating panels of stainless steel or Plexiglas and a steel grid floor. They contained 2 response levers with stimulus lights above them, a ceiling light, a food pellet dispenser, and a water bottle mounted outside. Tygon tubing connected a tether and swivel at the top of the cage to a syringe pump mounted outside a

wooden enclosure that surrounded the test chamber. Data collection and experimental programming were controlled by MED-PC software (Med Associates, St. Albans, VT).

**[1444]** As previously described (Perry et al., (2005) *Psychopharmacology (Berl)* **178**:193-201), the locomotor track was circular stainless steel, 71 cm diameter. It was equipped with 4 infrared sensors around the inner perimeter, at 0°, 90°, 180° and 270°, and connected to a VersaMax programmable logic controller (IC200UDR001, GE Fanuc Automation, Charlottesville, VA).

### *7. Surgical preparation for cocaine self-administration*

**[1445]** Under anesthesia with ketamine (60 mg/kg) and xylazine (10 mg/kg), with atropine (0.15 ml) and doxapram (5 mg/kg) to facilitate respiration, 15 rats were implanted with a 15-cm silastic catheter (0.51 mm i.d., 0.94 mm o.d.; Helix Medical Inc., Carpinteria, CA). The catheter, with 2 beads of prosthetic silicone elastomer, 3 and 3.5 cm from one end (MDX4-4210; Factor II, Inc. Lakeside, AZ), was introduced into the right jugular vein and anchored with sterile silk sutures. The free end was led to an exit incision medial and 1 cm caudal to the scapulae. Heparin (10 IU/kg i.v.) and gentomycin (12.0 mg/kg, i.v.) were administered for 3 days to prevent clotting.

### *8. Behavioral training and reinstatement*

**[1446]** The catheterized rats learned to lever press under a fixed ratio 1 (FR 1) schedule, which delivered 1 infusion of cocaine contingent upon 1 lever-press. Behavioral sessions began daily at 1 pm and ended at 3 pm. When responding had stabilized for 14 days, cocaine was replaced with physiologic saline. Self-administration behavior was then allowed to extinguish for 21-days, during which responses continued to produce infusion-related stimuli and saline infusions. Next followed a 3-day cue-extinction period in which the infusion pump and house light were disconnected in order to completely extinguish responding and ensure that reinstatement specifically reflected drug priming.

**[1447]** Subsequent reinstatement sessions involved no self-administration of cocaine or saline, or infusion-related stimuli. To begin each session, the experimenter administered an i.p. priming injection of saline (S), cocaine (C), or amphetamine (A) daily at 1 pm for 12 days according to the following sequence: S C S C S A S A S C S A. On the fourth (C) and sixth (A) day, the rats were pretreated at 9 am with 2 mg/kg Albu-CocH, administered through the infusion apparatus and flushed with 0.3 ml sterile saline.

### *9. Locomotor activity and food reinforced behavior*

**[1448]** Locomotor activity was assessed daily for 30 min beginning at 11:00 am by detecting

infrared beam breaks, as described by Perry et al. (2005). Two or more breaks of one beam occurring before another beam was broken were counted as a single response. After behavior stabilized (no steadily increasing or decreasing trends for 3 days), rats were injected at 9 am with saline (tail vein) for 4 days, then Albu-CocH for 1 day and saline again on the final day.

**[1449]** Rats were placed in the operant conditioning chambers for a 3-hr food session at 1:00 pm daily. Food pellets (45 mg) were contingent upon responses on either lever under a FR 1 adjusting delay discounting schedule (Perry et al. 2005). A response on the "immediate lever" produced 1 pellet immediately, while a "delay lever" response resulted in 3 pellets after a delay that altered during the session based on the animal's behavior. The delay started at 6 sec, and it increased by 1 sec after a "delay lever" response lever and decreased by 1 sec after an "immediate lever" response. The session ended on completion of 60 trials or after 3 hr, whichever came first. Following the session, rats were given additional food to reach a total of 16 g per day. Each day the delay started at the value it ended with the day before.

**[1450]** Each session was divided into fifteen 4-trial blocks. The first and second trials of each block were forced exposure to each lever (immediate and delayed condition in counterbalanced order), while the third and fourth trials were free choice, immediate or delayed, and a response on either lever yielded 1 or 3 pellets, respectively. A mean adjusted delay (MAD) was calculated by averaging the delays that were in effect on all of the free choice trials (maximum = 30) completed on the "delay" lever. MAD values served as a quantitative measure of impulsivity for food and provided another dimension of food-rewarded behavior in addition to amount of food earned.

### *10. Statistical analysis and pharmacokinetic calculations*

**[1451]** Blood pressure changes were analyzed statistically with StatView 4.5 (Abacus Concepts, Berkeley, CA). Treatment effects were subjected to 2-way analysis of variance with time and treatment as factors; $p < 0.05$ was considered statistically significant. Self-administration and other behavioral data were analyzed by one and two way analysis of variance followed by post-hoc testing. Enzyme plasma concentration-time profiles were analyzed with t Sigma Plot 4.1 (Jandel Scientific, Temecula CA), fitting the data to a bi-exponential decay curve that estimated terminal half-life. Enzyme kinetic data (V = velocity, S = substrate concentration) were analyzed by direct fit to the Michaelis-Menten equation: $V = Vmax^* (S/(S + Km))$.

## *C. Results*

**[1452]** Radiometric assay (see Methods) revealed a cocaine kcat (2700 ± 190 min-1) and Km (2. 1 ± 0.1 μM) similar to the unfused mutant (Pan et al., 2005). By comparison, the bacterial

enzyme is reported to have a kcat of 470 min-1, and a Km of 0.64 μM (Turner et al., 2002). Catalytic efficiency, measured as the ratio of kcat/Km, is therefore 75% higher in the mutated BChE.

**[1453]** When pure Albu-CocH was injected through the tail vein into male Wistar rats (250-300 g), it had no discernable effect at doses up to 3 mg/kg, while 10 mg/kg caused mild lethargy for 1 hour. Enzyme assays of repeated blood samples from 5 rats showed that the injected activity was stable, with a plasma half-life of 8 ± 0.5 hr (**Fig. 23**). Furthermore, Albu-CocH blocked pressor responses to a moderate dose of cocaine without lowering blood pressure on its own or opposing the pressor effects of norepinephrine (**Fig. 24**). These findings led to the hypothesis that Albu-CocH would be able to alleviate toxicity and overdose in humans. Testing that possibility in animals required the exposure of awake, unrestrained rats to doses of cocaine with a potential to evoke serious toxicity (defined as seizures).

**[1454]** Experience had shown that an i.p. challenge with cocaine (100 mg/kg) regularly induced convulsions that ended in death within 2 minutes unless euthanasia was administered. To minimize distress here, we followed an IACUC-approved protocol calling for euthanasia of any rat exhibiting continuous convulsion for 60 sec or convulsions of over 15 sec within a 2 min period. After receiving the cocaine challenge, each of ten unprotected rats developed head bobbing and hyperlocomotion followed by convulsions (onset time, 170 ± 30 sec), which met the euthanasia criterion. Pretreatment with i.v. Albu-CocH, however, provided dramatic, dose-dependent protection (**Fig. 25**). A small dose (1 mg/kg) delayed but did not prevent arousal or seizures in 4 of 4 rats (onset, 380 ± 70 sec); a mid-dose (3 mg/kg) prevented seizures but not signs of arousal (6 of 6 rats); a large dose (10 mg/kg) eliminated arousal and seizures (6 of 6 rats), and it raised cocaine's ED50 for this toxicity by nearly a factor of 10.

**[1455]** Not wishing to be bound by any theory, it seems that accelerated cocaine hydrolysis is the simplest explanation for this protection because the same cocaine challenge caused convulsions in all sham-treated animals (3 given 10 mg/kg human serum albumin and 2 given Albu-CocH inactivated by di-isopropylfluorophosphate, $10^{-4}$ M, 1 hr). The protection was specific to cocaine, as active enzyme at 10 mg/kg failed to delay or prevent convulsions in 3 rats challenged with amphetamine at the threshold dose (150 mg/kg) for producing uniform seizures in our unprotected rats. Protection against cocaine was lasting. No seizures occurred in any rat challenged up to 12 hr after receiving 10 mg/kg Albu-CocH (4 rats between 1 and 6 hr, and 4 at 12 hr). Of 5 rats challenged after 24 hr, 2 escaped seizures, 1 experienced seizures for 15 sec before recovering, and 2 experienced seizures that met the criterion for euthanasia. Thus, in this

experiment, 24 hours marked the outer limit of protection.

**[1456]** Human overdose requires rescue. To evaluate rescue potential in rats 100 mg/kg of cocaine was injected into rats. When the onset of convulsions began, the rats were then rapidly administered Albu-CocH (3 or 10 mg/kg). Each of three rats given 10 mg/kg ceased convulsing within 1 min, resumed an upright posture within 2 min, and showed no further signs of cocaine-induced arousal. Thereafter, apart from lethargy and mild paw swelling for 1 to 2 hour ("hr"), they resembled untreated controls. Three of three rats given 3 mg/kg also ceased convulsing within 1 min and quickly regained upright posture. These animals exhibited head bobbing and hyperlocomotion for approximately 1 hr. On the next day both treated groups were indistinguishable from rats that never received cocaine. At 10 mg/kg, Albu-CocH was also partially effective against a larger cocaine overdose, saving 4 of 6 rats challenged with 300 mg/kg of i.p. cocaine. In contrast, wild-type BChE, 3 mg/kg, was ineffective at rescue in 3 of 3 rats even after standard cocaine challenge (100 mg/kg), all of which met our criterion for early euthanasia.

**[1457]** These results established dose-dependent and hydrolase-specific rescue from cocaine intoxication. The rescue was rapid for an agent largely excluded from the brain (tissue activity < 1% of plasma activity) and thought to act by eliminating free cocaine and promoting drug dissociation from tissues. Additionally, Albu-CocH removed cocaine from plasma almost instantly. In 4 control rats treated with $^{3}$H-cocaine (3.5 mg/kg, i.v.), plasma drug half-life was 50 ± 5 min, but in 4 rats given 3 mg/kg Albu-CocH 10 min beforehand, 98% of the free drug was converted to benzoic acid within 30 sec (**Fig. 26**), and the drug burden in heart and brain was greatly reduced (**Fig. 27**).

**[1458]** An enzyme powerful enough to rescue rats from cocaine toxicity might also be useful in reducing drug-reward and managing cocaine addiction. To evaluate that possibility, Albu-CocH was tested in rats that had been trained to self-administer cocaine. One of the most refractory and troublesome aspects of cocaine addiction is relapse after abstinence. One goal was to determine whether fast metabolism of cocaine *en route* to brain reward centers could prevent relapse triggered by an i.v. priming injection of cocaine. The effect of Albu-CocH pretreatment on the cocaine-primed reinstatement of drug-seeking behavior in rats that had previously self-administered cocaine and subsequently extinguished their responding when saline replaced cocaine, was examined.

**[1459]** Rats were trained to emit one lever press for each cocaine infusion (0.4 mg/kg, i.v.) during daily sessions under a fixed-ratio 1 (FR 1) schedule. After behavior stabilized for 14 days,

saline was substituted for cocaine for 21 days, and behavior was allowed to extinguish. In a subsequent reinstatement phase, priming injections of cocaine were given (alternating daily with saline priming injections). On selected days, rats received Albu-CocH (2 mg/kg) 2 hr before the reinstatement session. Cocaine priming injections (10 mg/kg, i.p.) generated 30-40 responses on the 2 days with no pretreatment (**Fig. 28**). After Albu-CocH, however, cocaine priming caused negligible responding. Saline priming on intervening days resulted in minimal responses (2-5) on the lever previously associated with cocaine. To control for possible nonspecific behavioral suppression, we also tested priming injections of d-amphetamine, which is not a hydrolase substrate. Amphetamine primes (2 mg/kg, i.p.) elicited ≈ 60 reinstatement responses, which, consistent with an effect that depended on selective metabolism, were not significantly reduced by Albu-CocH.

**[1460]** To further confirm that Albu-CocH did not cause generalized behavioral suppression that might impair reinstatement after cocaine-priming, the effect of Albu-CocH on locomotor activity and responding for food was investigated. For these studies, 5 rats were treated alternately with i.v. saline, Albu-CocH, and saline. Two hr after each day's injection, locomotion was monitored in a circular open field with 4 infrared beams equally spaced around the perimeter (Piazza et al., (1989) *Behav Brain Res* 31:267-271). The beam break data showed no treatment effect (Table 17).

**[1461]** Four hours after the saline or enzyme injections, the same rats were studied in an operant conditioning experiment with food delivery contingent upon FR 1 lever-press responding in a paradigm designed to assess impulsivity for reward (Perry et al., 2005). This task involved 2 levers. One lever immediately produced a single 45 mg food pellet and the other produced 3 pellets after a delay. The delay began at 6 sec, and it increased by 1 sec after each response on the delay lever, and decreased by 1 sec after each response on the immediate lever. Results after Albu-CocH showed no significant differences (vs. saline) in trials completed, number of pellets earned, food intake, or mean adjusted delay for the 60 choice trials (Table 17).

| | Locomotor | Food-reinforced Behavior | | | |
|---|---|---|---|---|---|
| Injections | Beam Breaks | Trials Completed | No. of Pellets | Food Intake (g) | Mean adjusted delay* (sec) |
| Saline | 23.8 ± 2.4 | 57.2 ± 2.8 | 110 ± 4.9 | 4.93 ± 2.2 | 14.0 ± 5.0 |

| | | | | | |
|---|---|---|---|---|---|
| Albu-CocH | 21.2 ± 4.2 | 57.8 ± 1.4 | 115 ± 6.2 | 5.15 ± 2.7 | 7.44 ± 0.45 |
| Saline | 21.0 ± 2.6 | 54.2 ± 5.8 | 108 ± 10.3 | 4.88 ± 4.6 | 6.84 ± 1.5 |

* self-determined measure of impulsivity for food

**Table 17.** Albu-CocH does not alter locomotor activity or food-reinforced responding. Five rats received saline or Albu-CocH at 9 am on 3 consecutive days. Mean values (± SEM) shown for locomotor activity (11 am) and food-rewarded behavior (1 pm). The enzyme treatment had no statistically significant effect.

**[1462]** BChE-catalyzed cocaine hydrolysis generates two breakdown products, benzoic acid and ecgonine methyl ester. As compared with other metabolites, including norcocaine and benzylecgonine, these products have greatly reduced biologic activity. Thus, the reaction is detoxifying.

**[1463]** These results illustrate that BChE-albumin fusions can prevent cocaine access to critical biological targets, including heart and brain, and, while not wishing to be bound by any theory, suggest that rescue injections create steep diffusion gradients favoring the loss of cocaine from sites throughout the body and especially from brain, with its high regional blood flow. Hence Albu-CocH is well suited for the emergency treatment of cocaine overdose.

**[1464]** In addition to emergency uses, the repeated or continuous delivery of Albu-CocH would help addicts avoid the full relapse that commonly follows a brief lapse. Long plasma half-life is desirable for such a purpose. Allometric scaling from the rat data, in light of experience with other albumin fusion proteins, is compatible with a several-day half-life of Albu-CocH in humans, allowing sustained acceleration of cocaine hydrolysis with a view to preventing relapse.

**[1465]** Relapse or "reinstatement" is perhaps the greatest challenge in treating drug abuse. Drug-seeking behavior in established animal models of reinstatement is regularly triggered by exposure to drug-associated environmental cues. Factors that predict or enhance reinstatement include female sex, estrogen status, higher drug dose, addiction-prone phenotypes such as impulsivity or sweet-preference, and food restriction. Especially powerful are "priming exposures" of drugs with related pharmacological mechanisms. The above experiments show that Albu-CocH was fully effective in blocking reinstatement provoked by cocaine-priming injections.

**[1466]** Under conditions like those that produced reinstatement of cocaine-primed, cocaine-seeking behavior, Albu-CocH did not affect locomotor behavior, food-rewarded behavior,

impulsivity for food, or amphetamine-primed reinstatement. These results from an animal model of relapse support the hypothesis that, by preventing cocaine access to the brain, accelerated metabolism can blunt not only toxicity, but also the reward-seeking effects of this drug. The virtual elimination of cocaine-primed reinstatement suggests that sustained delivery of an efficient hydrolase would reduce the probability of relapse in recovering addicts even though it did not suppress craving. As to administration, it is likely that weekly administration of BChE-albumin fusions could provide continuous, rapid elimination of cocaine as a therapy of cocaine addiction. Furthermore, additional modifications of the protein may provide even better pharmacokinetics.

**[1467]** Additionally or alternatively, viral gene transduction of a BChE albumin fusion may be used as a therapeutic strategy. It has been shown that standard E1-deleted adenoviral vectors sustain effective levels of a cocaine hydrolase for days in the rat bloodstream and brain, while ongoing work with a helper-dependent adenoviral vector is showing expression windows of months or more.

**[1468]** The entire disclosure of each document cited (including patents, patent applications, patent publications, journal articles, abstracts, laboratory manuals, books, or other disclosures) as well as information available through Identifiers specific to databases such as GenBank, GeneSeq, or the CAS Registry, referred to in this application are herein incorporated by reference in their entirety.

**[1469]** Furthermore, the specification and sequence listing of each of the following International applications and U.S. applications are herein incorporated by reference in their entirety: International Application No. PCT/US02/40891, filed December 23, 2002; International Applicaiton No. PCT/US2004/001369, filed January 20, 2004; International Application No. PCT/US2005/004041, filed February 9, 2005; U.S. Application No. 10/775,204, filed February 11, 2004; U.S. Application No. 11/175,690, filed July 7, 2005; U.S. Application No. 11/429,373, filed May 8, 2006; U.S. Application No. 11/429,276, filed May 8, 2006; U.S. Application No. 11/429,374, filed May 8, 2006; and U.S. Provisional Application Nos. 60/707,521, filed August 12, 2005; 60/712,386, filed August 31, 2005; 60/732,724, filed November 3, 2005; 60/776,914, filed February 28, 2006; 60/781,361, filed March 13, 2006; and 60/810,182, filed June 2, 2006, and 60/813,682, filed June 15, 2006.

Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or method step or group of elements or integers or method steps but not the exclusion of any element or integer or method step or group of elements or integers or method steps.

Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

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**CLAIMS:**

1. A method of reducing reward-seeking effects of cocaine in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising Albu-CocH, wherein said mammal is a cocaine addict.

2. The method of Claim 1, wherein said method prevents relapse of said cocaine addict after cocaine abstinence.

3. The method of any one of Claims 1 or 2, wherein said pharmaceutical composition accelerates cocaine hydrolysis in said mammal.

4. The method of any one of the previous claims, wherein said pharmaceutical composition reduces cocaine access to a biological target of cocaine in said mammal.

5. The method of Claim 4, wherein said biological target of cocaine is the heart.

6. The method of Claim 4, wherein said biological target of cocaine is the brain.

7. A method of managing cocaine addiction in a mammal, comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising Albu-CocH, wherein the mammal was once addicted to cocaine.

8. The method of Claim 7, wherein said pharmaceutical composition is administered before said mammal ingests cocaine.

9. The method of claim any one of Claims 7 or 8, wherein administration of the pharmaceutical composition reduces a probability of relapse after cocaine abstinence.

10. The method of any one of Claims 7 to 9, wherein said pharmaceutical composition accelerates cocaine hydrolysis in said mammal.

11. The method of any one of Claims 7 to 10, wherein said pharmaceutical composition reduces cocaine access to a biological target of cocaine in said mammal.

12. The method of Claim 11, wherein said biological target of cocaine is the heart.

13. The method of Claim 11, wherein said biological target of cocaine is the brain

14. A method according to any one of Claims 1 to 13 substantially as herein described with reference to the Figures and/or Examples.

```
  1 GAT GCA CAC AAG AGT GAG GTT GCT CAT CGG TTT AAA GAT TTG GGA GAA GAA AAT TTC AAA 60
  1 D   A   H   K   S   E   V   A   H   R   F   K   D   L   G   E   E   N   F   K   20

 61 GCC TTG GTG TTG ATT GCC TTT GCT CAG TAT CTT CAG CAG TGT CCA TTT GAA GAT CAT GTA 120
 21 A   L   V   L   I   A   F   A   Q   Y   L   Q   Q   C   P   F   E   D   H   V   40

121 AAA TTA GTG AAT GAA GTA ACT GAA TTT GCA AAA ACA TGT GTT GCT GAT GAG TCA GCT GAA 180
 41 K   L   V   N   E   V   T   E   F   A   K   T   C   V   A   D   E   S   A   E   60

181 AAT TGT GAC AAA TCA CTT CAT ACC CTT TTT GGA GAC AAA TTA TGC ACA GTT GCA ACT CTT 240
 61 N   C   D   K   S   L   H   T   L   F   G   D   K   L   C   T   V   A   T   L   80

241 CGT GAA ACC TAT GGT GAA ATG GCT GAC TGC TGT GCA AAA CAA GAA CCT GAG AGA AAT GAA 300
 81 R   E   T   Y   G   E   M   A   D   C   C   A   K   Q   E   P   E   R   N   E   100

301 TGC TTC TTG CAA CAC AAA GAT GAC AAC CCA AAC CTC CCC CGA TTG GTG AGA CCA GAG GTT 360
101 C   F   L   Q   H   K   D   D   N   P   N   L   P   R   L   V   R   P   E   V   120

361 GAT GTG ATG TGC ACT GCT TTT CAT GAC AAT GAA GAG ACA TTT TTG AAA AAA TAC TTA TAT 420
121 D   V   M   C   T   A   F   H   D   N   E   E   T   F   L   K   K   Y   L   Y   140

421 GAA ATT GCC AGA AGA CAT CCT TAC TTT TAT GCC CCG GAA CTC CTT TTC TTT GCT AAA AGG 480
141 E   I   A   R   R   H   P   Y   F   Y   A   P   E   L   L   F   F   A   K   R   160
```

Figure 1A

```
481 TAT AAA GCT GCT TTT ACA GAA TGT TGC CAA GCT GCT GAT AAA GCT GCC TGC CTG TTG CCA 540
161 Y  K  A  A  F  T  E  C  C  Q  A  A  D  K  A  A  C  L  L  P  180

541 AAG CTC GAT GAA CTT CGG GAT GAA GGG AAG GCT TCG TCT GCC AAA CAG AGA CTC AAA TGT 600
181 K  L  D  E  L  R  D  E  G  K  A  S  S  A  K  Q  R  L  K  C  200

601 GCC AGT CTC CAA AAA TTT GGA GAA AGA GCT TTC AAA GCA TGG GCA GTG GCT CGC CTG AGC 660
201 A  S  L  Q  K  F  G  E  R  A  F  K  A  W  A  V  A  R  L  S  220

661 CAG AGA TTT CCC AAA GCT GAG TTT GCA GAA GTT TCC AAG TTA GTG ACA GAT CTT ACC AAA 720
221 Q  R  F  P  K  A  E  F  A  E  V  S  K  L  V  T  D  L  T  K  240

721 GTC CAC ACG GAA TGC TGC CAT GGA GAT CTG CTT GAA TGT GCT GAT GAC AGG GCG GAC CTT 780
241 V  H  T  E  C  C  H  G  D  L  L  E  C  A  D  D  R  A  D  L  260

781 GCC AAG TAT ATC TGT GAA AAT CAG GAT TCG ATC TCC AGT AAA CTG AAG GAA TGC TGT GAA 840
261 A  K  Y  I  C  E  N  Q  D  S  I  S  S  K  L  K  E  C  C  E  280

841 AAA CCT CTG TTG GAA AAA TCC CAC TGC ATT GCC GAA GTG GAA AAT GAT GAG ATG CCT GCT 900
281 K  P  L  L  E  K  S  H  C  I  A  E  V  E  N  D  E  M  P  A  300

901 GAC TTG CCT TCA TTA GCT GCT GAT TTT GTT GAA AGT AAG GAT GTT TGC AAA AAC TAT GCT 960
301 D  L  P  S  L  A  A  D  F  V  E  S  K  D  V  C  K  N  Y  A  320
```

Figure 1B

```
 961 GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT 1020
 321 E   A   K   D   V   F   L   G   M   F   L   Y   E   Y   A   R   R   H   P   D   340

1021 TAC TCT GTC GTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 1080
 341 Y   S   V   V   L   L   R   L   A   K   T   Y   E   T   T   L   E   K   C   360

1081 TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT 1140
 361 C   A   A   A   D   P   H   E   C   Y   A   K   V   F   D   E   F   K   P   L   380

1141 GTG GAA GAG GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 1200
 381 V   E   E   P   Q   N   L   I   K   Q   N   C   E   L   F   E   Q   L   G   E   400

1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260
 401 Y   K   F   Q   N   A   L   L   V   R   Y   T   K   K   V   P   Q   V   S   T   420

1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320
 421 P   T   L   V   E   V   S   R   N   L   G   K   V   G   S   K   C   C   K   H   440

1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380
 441 P   E   A   K   R   M   P   C   A   E   D   Y   L   S   V   V   L   N   Q   L   460

1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440
 461 C   V   L   H   E   K   T   P   V   S   D   R   V   T   K   C   C   T   E   S   480
```

Figure 1C

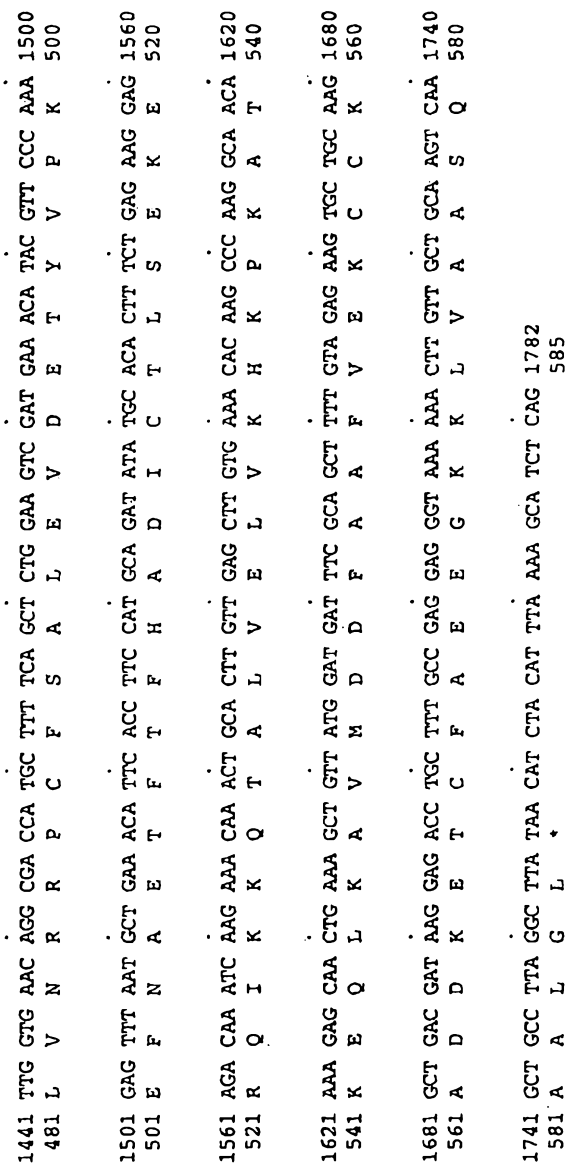

1441 TTG GTG AAC AGG CGA CCA TGC TTT TCA GCT CTG GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500
481 L V N R R P C F S A L E V D E T Y V P K 500
1501 GAG TTT AAT GCT GAA ACA TTC ACC TTC CAT GCA GAT ATA TGC ACA CTT TCT GAG AAG GAG 1560
501 E F N A E T F T F H A D I C T L S E K E 520
1561 AGA CAA ATC AAG AAA CAA ACT GCA CTT GTT GAG CTT GTG AAA CAC AAG CCC AAG GCA ACA 1620
521 R Q I K K Q T A L V E L V K H K P K A T 540
1621 AAA GAG CAA CTG AAA GCT GTT ATG GAT GAT TTC GCA GCT TTT GTA GAG AAG TGC TGC AAG 1680
541 K E Q L K A V M D D F A A F V E K C C K 560
1681 GCT GAC GAT AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT GCT GCA AGT CAA 1740
561 A D D K E T C F A E E G K K L V A A S Q 580
1741 GCT GCC TTA GGC TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782
581 A A L G L * 585

Figure 1D

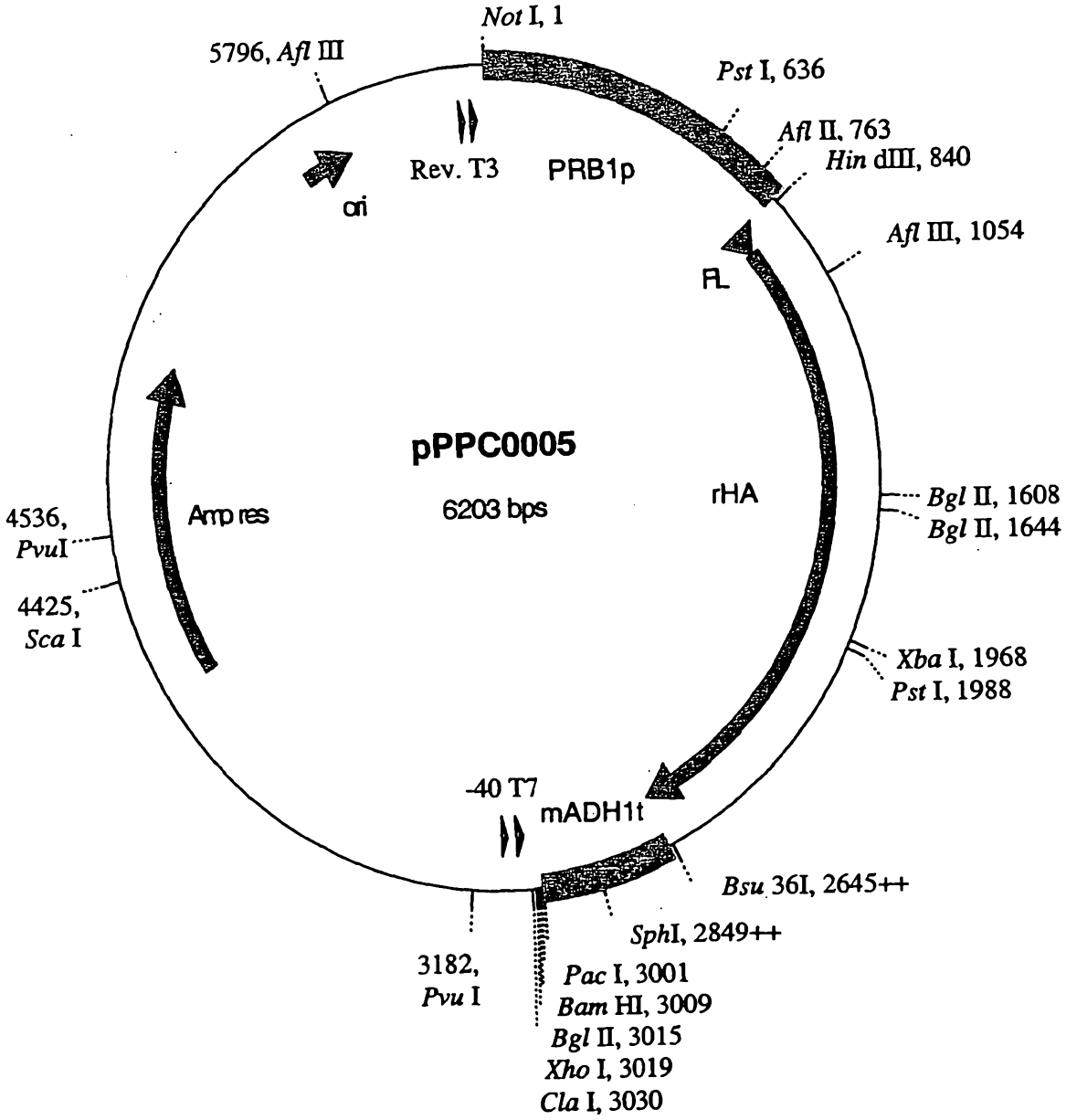

Not I, 1
Pst I, 636
Afl II, 763
Hin dIII, 840
Afl III, 1054
Bgl II, 1608
Bgl II, 1644
Xba I, 1968
Pst I, 1988
Bsu 36I, 2645++
SphI, 2849++
Pac I, 3001
Bam HI, 3009
Bgl II, 3015
Xho I, 3019
Cla I, 3030
3182, Pvu I
4425, Sca I
4536, PvuI
5796, Afl III
Rev. T3
PRB1p
ori
FL
rHA
mADH1t
-40 T7
Amp res
pPPC0005
6203 bps

**Figure 2**

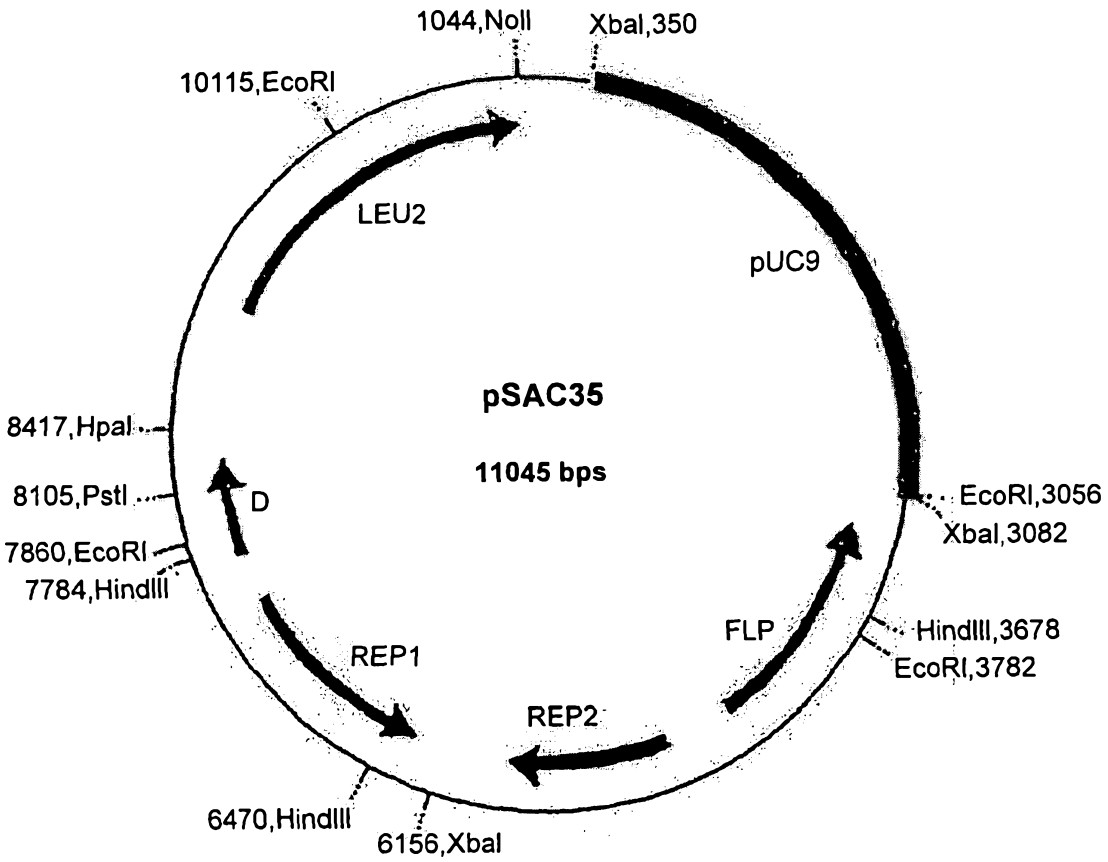

1044,NoII
XbaI,350
10115,EcoRI
LEU2
pUC9
pSAC35
11045 bps
8417,HpaI
8105,PstI
D
7860,EcoRI
7784,HindIII
EcoRI,3056
XbaI,3082
FLP
HindIII,3678
EcoRI,3782
REP1
REP2
6470,HindIII
6156,XbaI

**Figure 3**

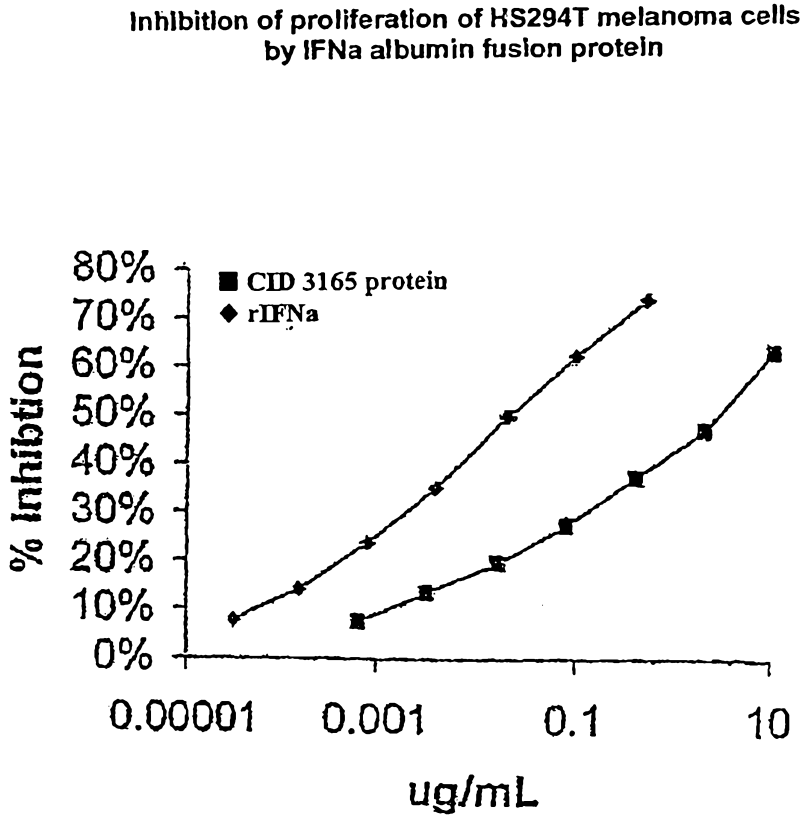

Inhibition of proliferation of HS294T melanoma cells
by IFNa albumin fusion protein
80%
70%
60%
50%
40%
30%
20%
10%
0%
% Inhibition
CID 3165 protein
rIFNa
0.00001
0.001
0.1
10
ug/mL

Figure 4

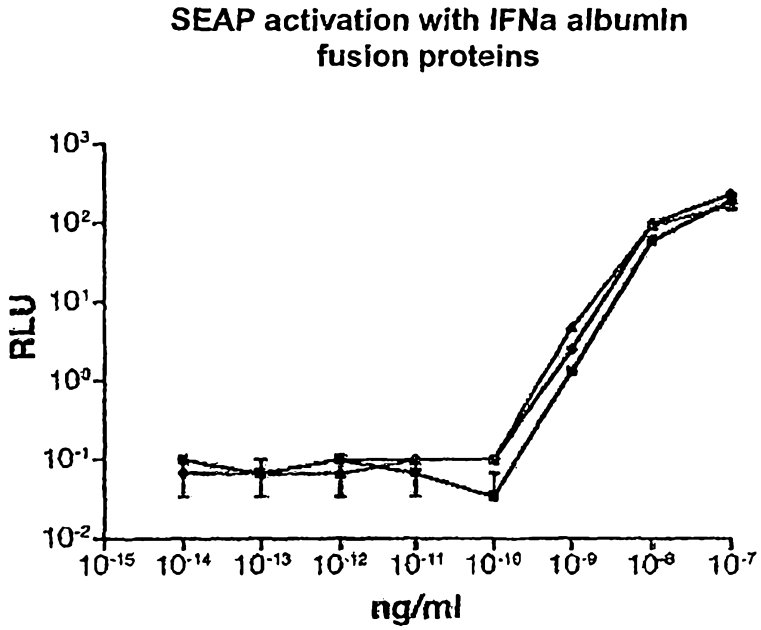

SEAP activation with IFNa albumin fusion proteins
RLU
$10^{3}$
$10^{2}$
$10^{1}$
$10^{0}$
$10^{-1}$
$10^{-2}$
$10^{-15}$ $10^{-14}$ $10^{-13}$ $10^{-12}$ $10^{-11}$ $10^{-10}$ $10^{-9}$ $10^{-8}$ $10^{-7}$
ng/ml

Figure 5

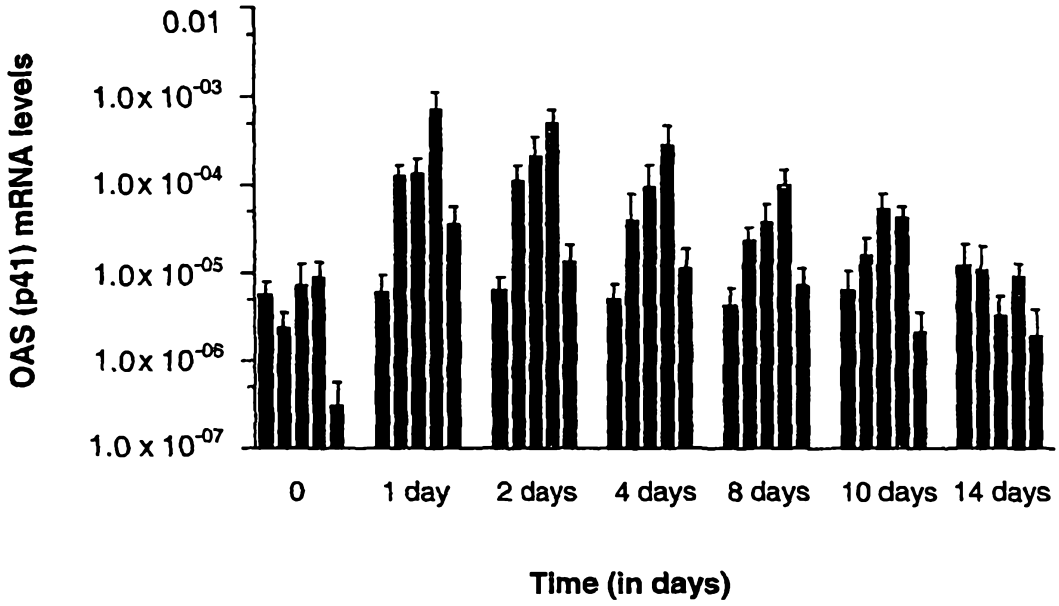

OAS (p41) mRNA levels
0.01
1.0x 10-03
1.0x 10-04
1.0x 10-05
1.0x 10-06
1.0 x 10-07
0
1 day
2 days
4 days
8 days
10 days
14 days
Time (in days)

**Figure 6**

Dose-response of recombinant BNP and BNP Albumin Fusion Proteins – BNP-HSA and BNP(2X)-HSA

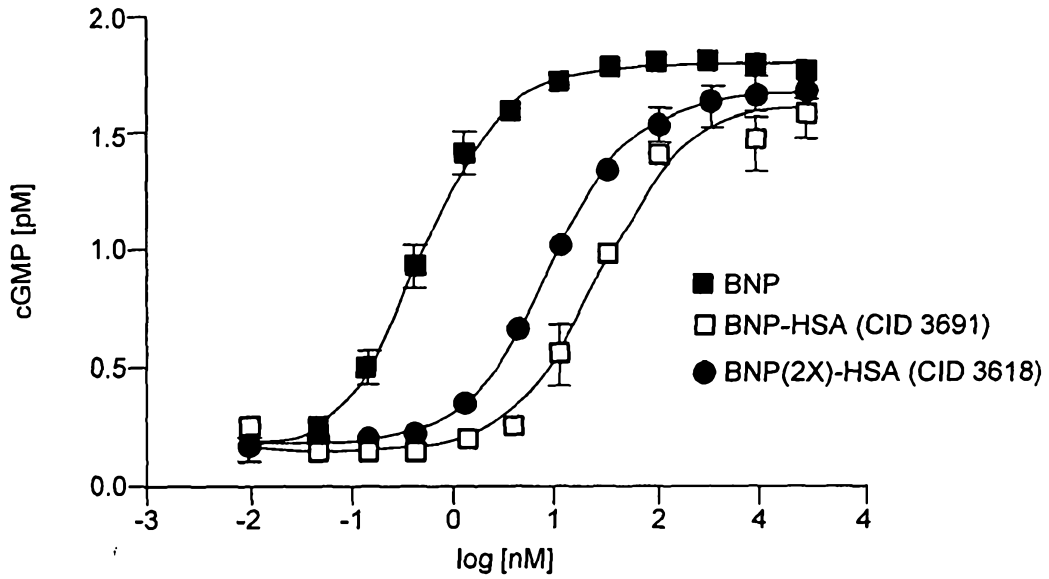



**Figure 7**

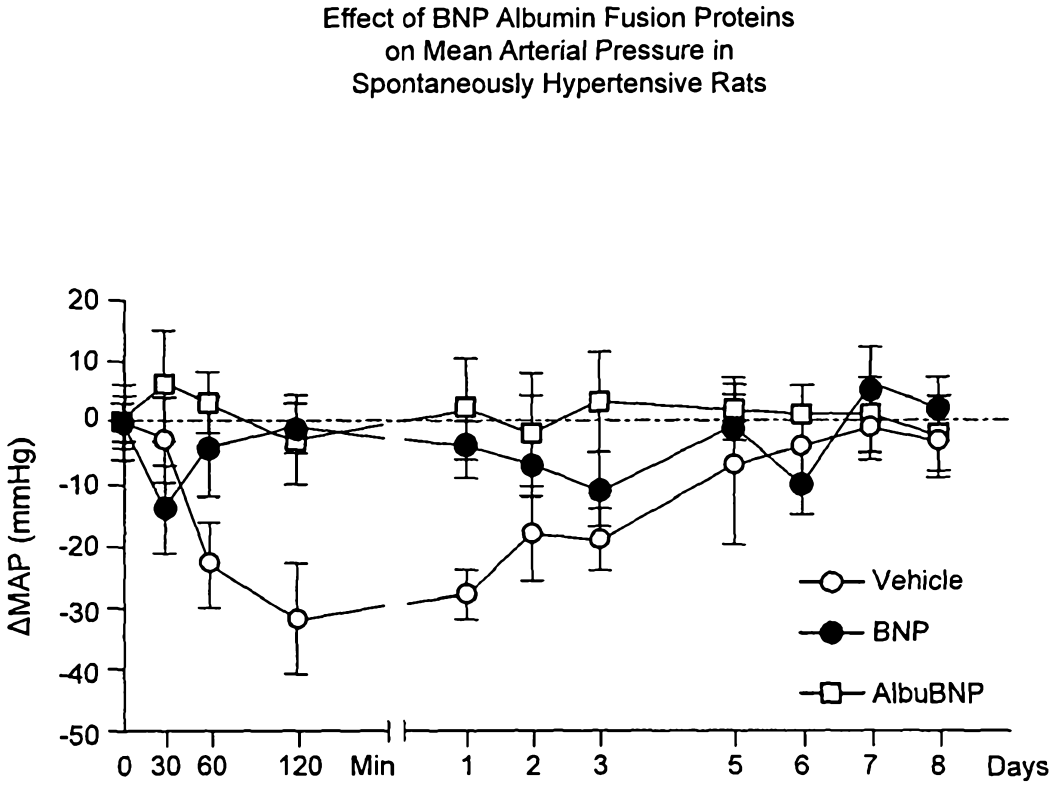

Effect of BNP Albumin Fusion Proteins
on Mean Arterial Pressure in
Spontaneously Hypertensive Rats
ΔMAP (mmHg)
20
10
0
-10
-20
-30
-40
-50
0 30 60 120 Min 1 2 3 5 6 7 8 Days
Vehicle
BNP
AlbuBNP

**Figure 8**

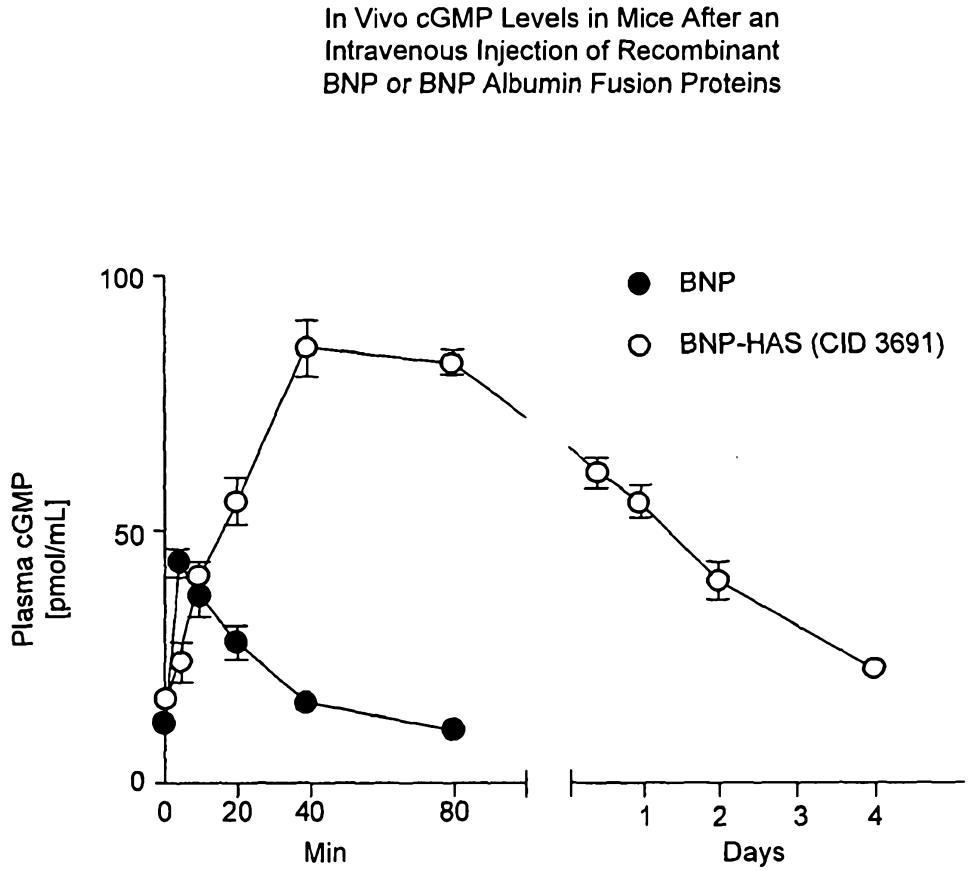
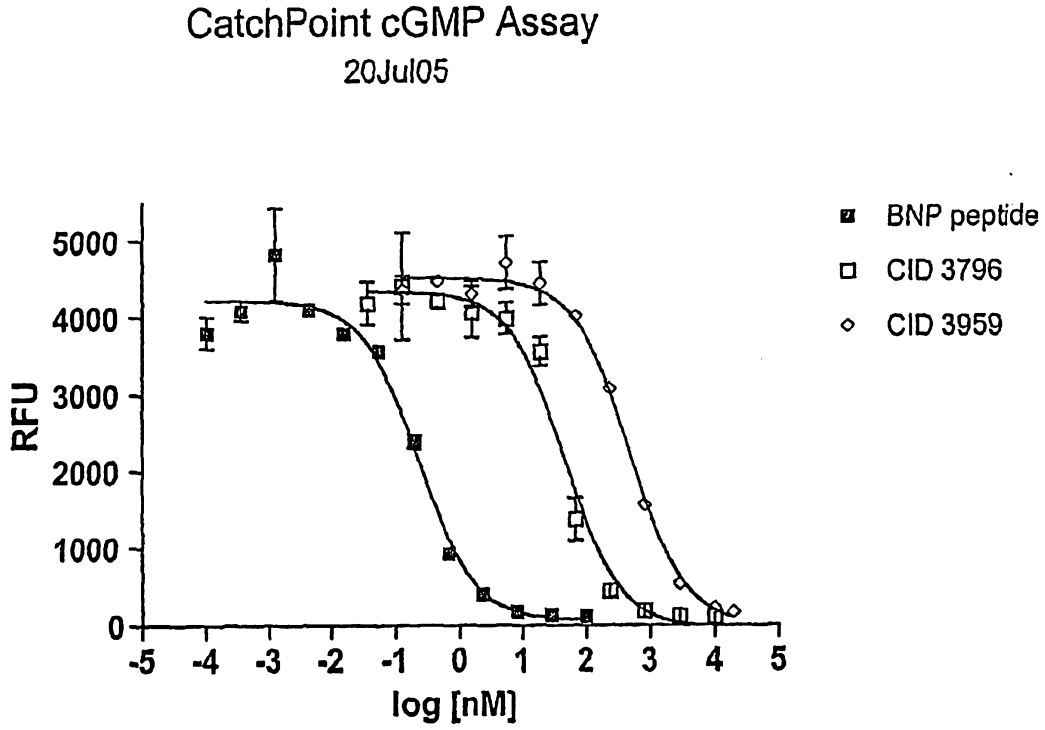
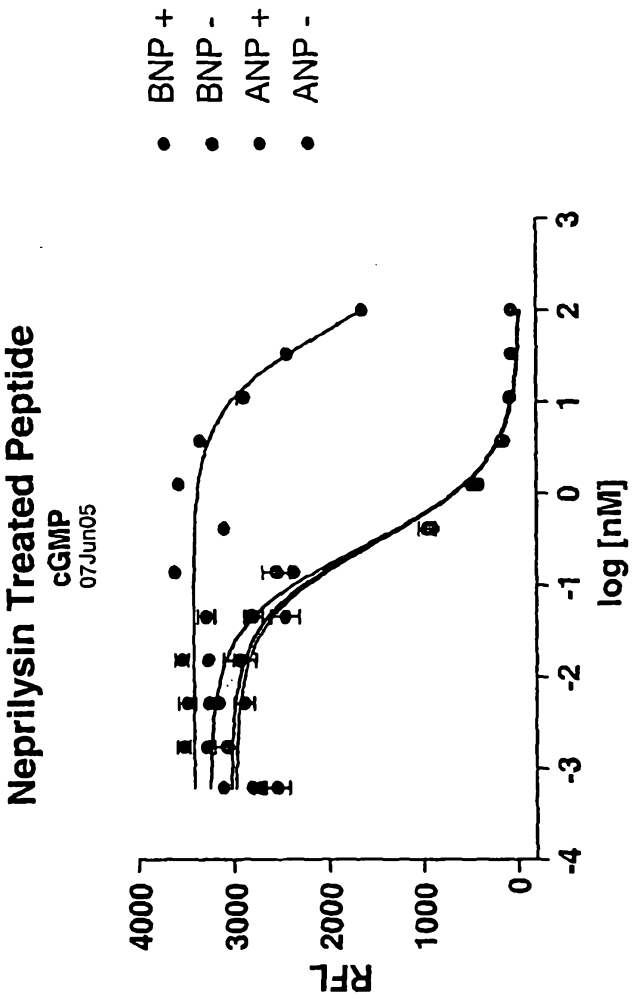

In Vivo cGMP Levels in Mice After an Intravenous Injection of Recombinant BNP or BNP Albumin Fusion Proteins
BNP
BNP-HAS (CID 3691)
Plasma cGMP [pmol/mL]
100
50
0
0
20
40
80
Min
1
2
3
4
Days

**Figure 9**




| | EC50 |
|---|---|
| CID 3796 | 45.06 |
| BNP peptide | 0.222-7 |
| Cid 3959 | 467.9 |

**Figure 10**




| | BNP + | BNP - | ANP + | ANP - |
|---|---|---|---|---|
| EC50 | 0.2966 | 0.2702 | 60.47 | 0.2965 |

Figure 11A

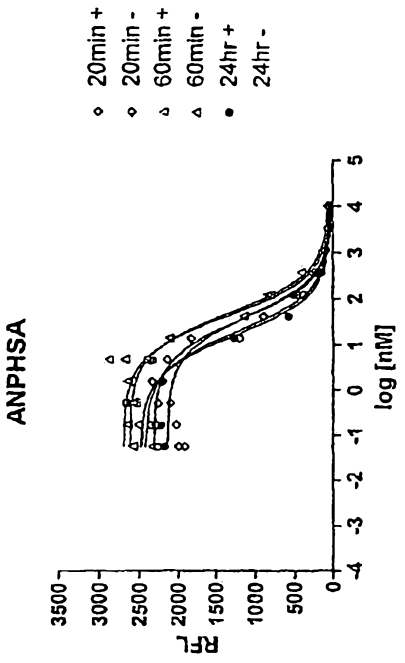



Figure 11C

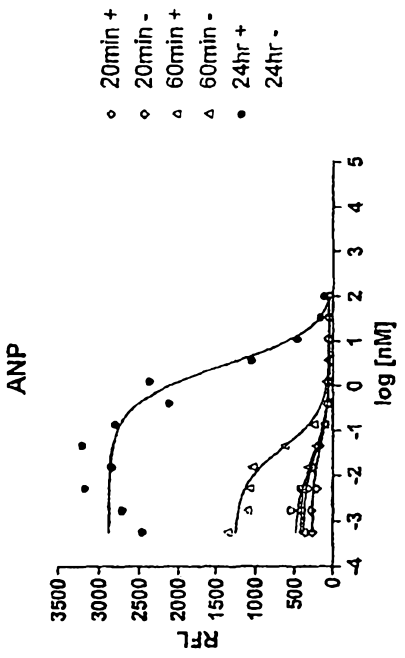



Figure 11B

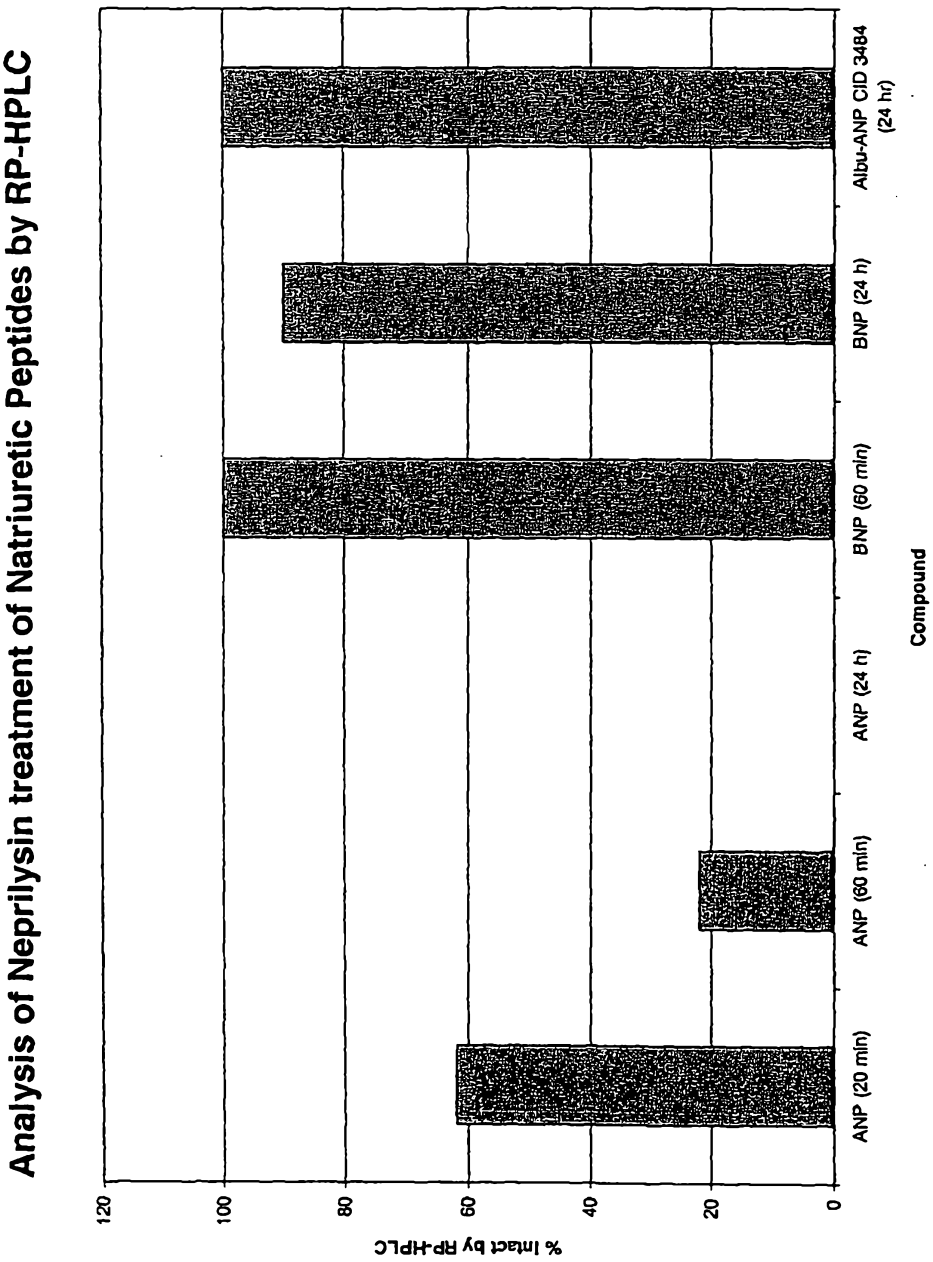

Analysis of Neprilysin treatment of Natriuretic Peptides by RP-HPLC
% Intact by RP-HPLC
120
100
80
60
40
20
0
ANP (20 min)
ANP (60 min)
ANP (24 h)
BNP (60 min)
BNP (24 h)
Albu-ANP CID 3484 (24 hr)
Compound

Figure 11D

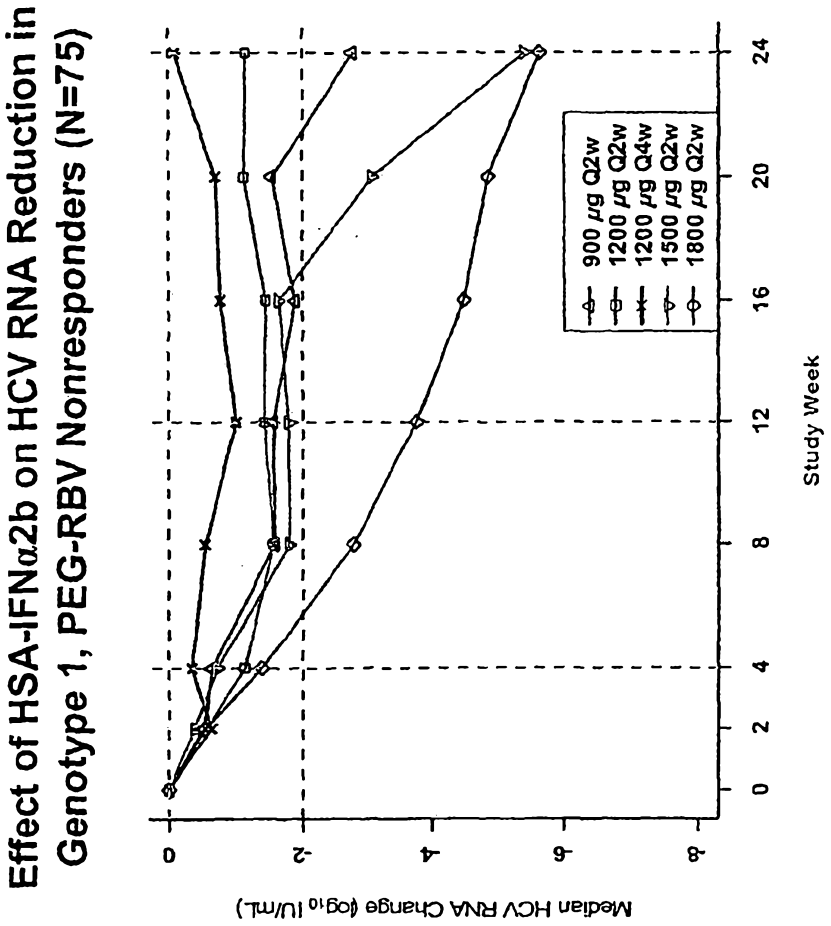

Effect of HSA-IFNα2b on HCV RNA Reduction in Genotype 1, PEG-RBV Nonresponders (N=75)
Median HCV RNA Change ($log_{10}$ IU/mL)
0
-2
-4
-6
-8
0
2
4
8
12
16
20
24
Study Week
900 μg Q2w
1200 μg Q2w
1200 μg Q4w
1500 μg Q2w
1800 μg Q2w

Figure 12

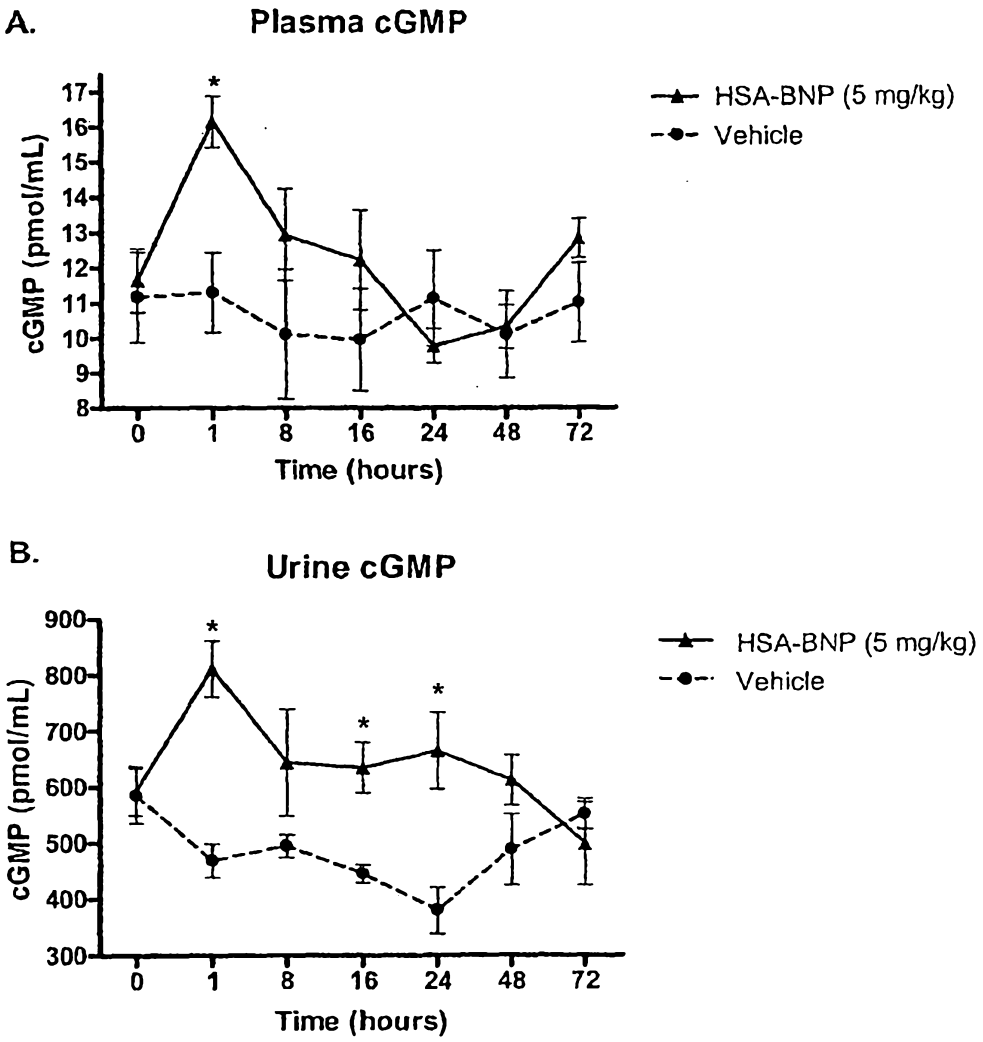

A.
Plasma cGMP
cGMP (pmol/mL)
17
16
15
14
13
12
11
10
9
8
0
1
8
16
24
48
72
Time (hours)
HSA-BNP (5 mg/kg)
Vehicle
B.
Urine cGMP
cGMP (pmol/mL)
900
800
700
600
500
400
300
0
1
8
16
24
48
72
Time (hours)
HSA-BNP (5 mg/kg)
Vehicle

Figure 13

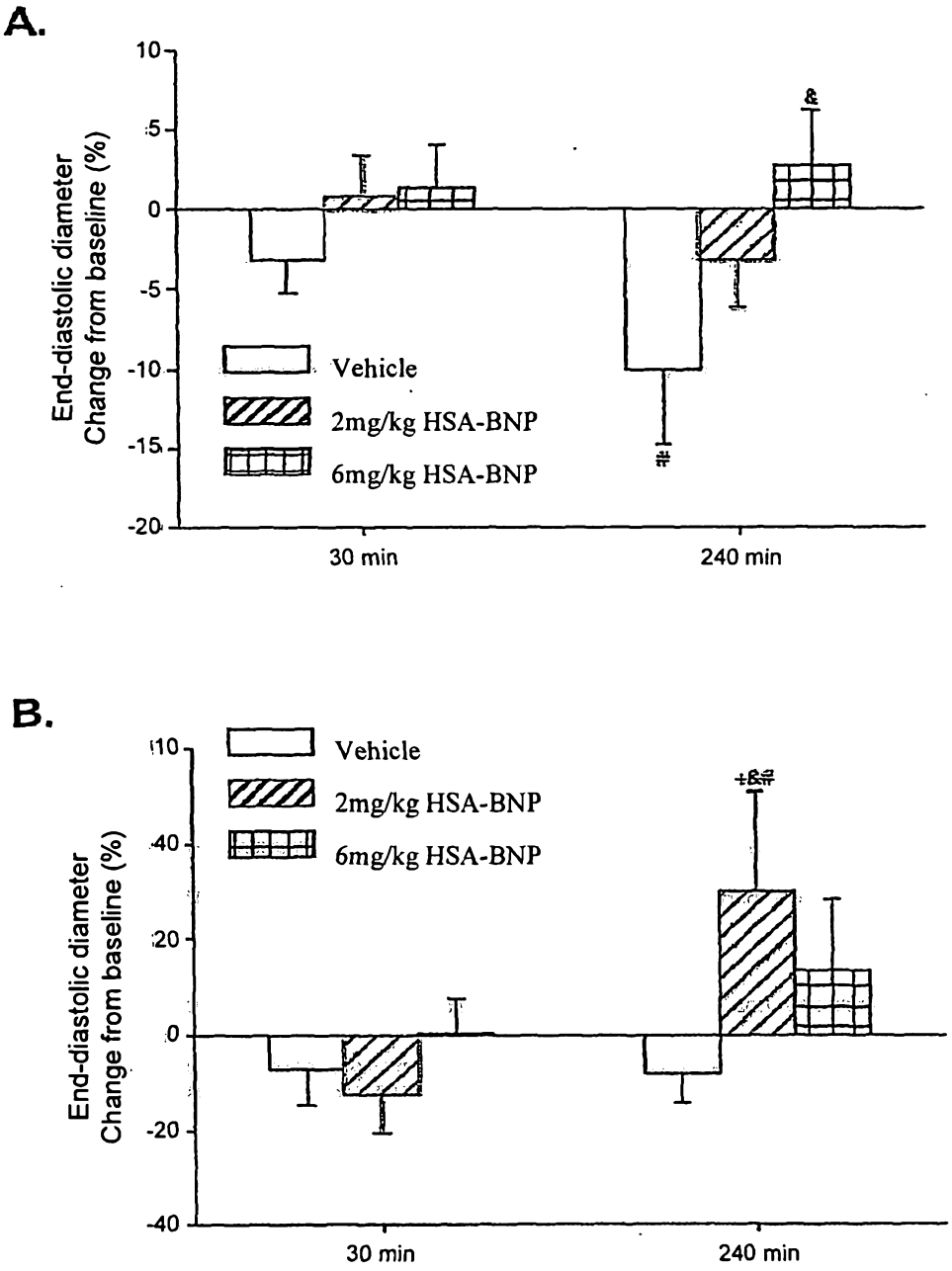

A.
End-diastolic diameter
Change from baseline (%)
10
5
0
-5
-10
-15
-20
Vehicle
2mg/kg HSA-BNP
6mg/kg HSA-BNP
#
&
30 min
240 min
B.
End-diastolic diameter
Change from baseline (%)
40
20
0
-20
-40
Vehicle
2mg/kg HSA-BNP
6mg/kg HSA-BNP
+&#
30 min
240 min

**Figure 14**

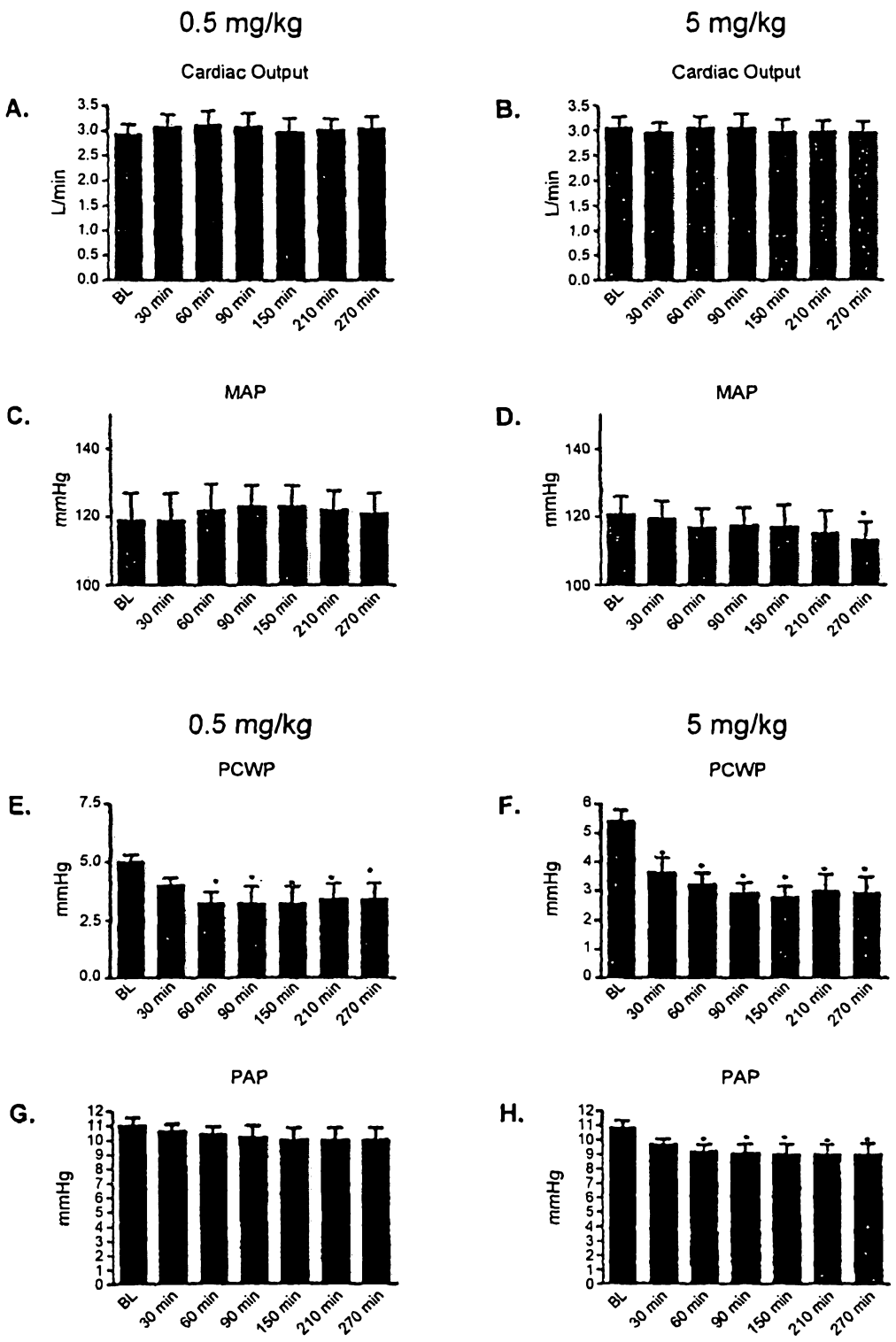

0.5 mg/kg
5 mg/kg
Cardiac Output
A.
B.
L/min
MAP
C.
D.
mmHg
PCWP
E.
F.
PAP
G.
H.
BL
30 min
60 min
90 min
150 min
210 min
270 min

**Figure 15**

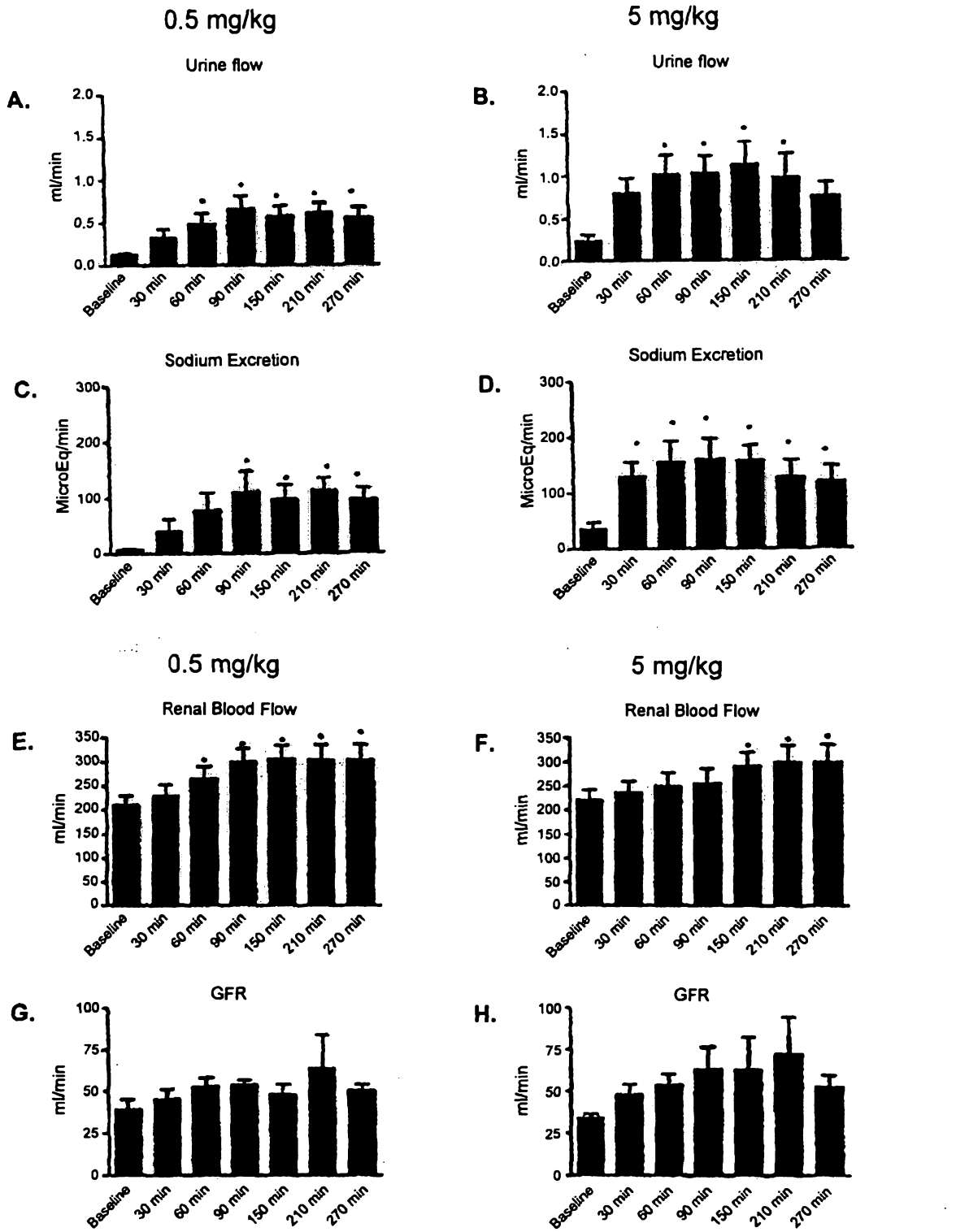

0.5 mg/kg
5 mg/kg
A.
Urine flow
ml/min
2.0
1.5
1.0
0.5
0.0
B.
Urine flow
ml/min
C.
Sodium Excretion
MicroEq/min
300
200
100
0
D.
Sodium Excretion
MicroEq/min
0.5 mg/kg
5 mg/kg
E.
Renal Blood Flow
ml/min
350
300
250
200
150
100
50
0
F.
Renal Blood Flow
ml/min
G.
GFR
ml/min
100
75
50
25
0
H.
GFR
ml/min
Baseline
30 min
60 min
90 min
150 min
210 min
270 min

**Figure 16**

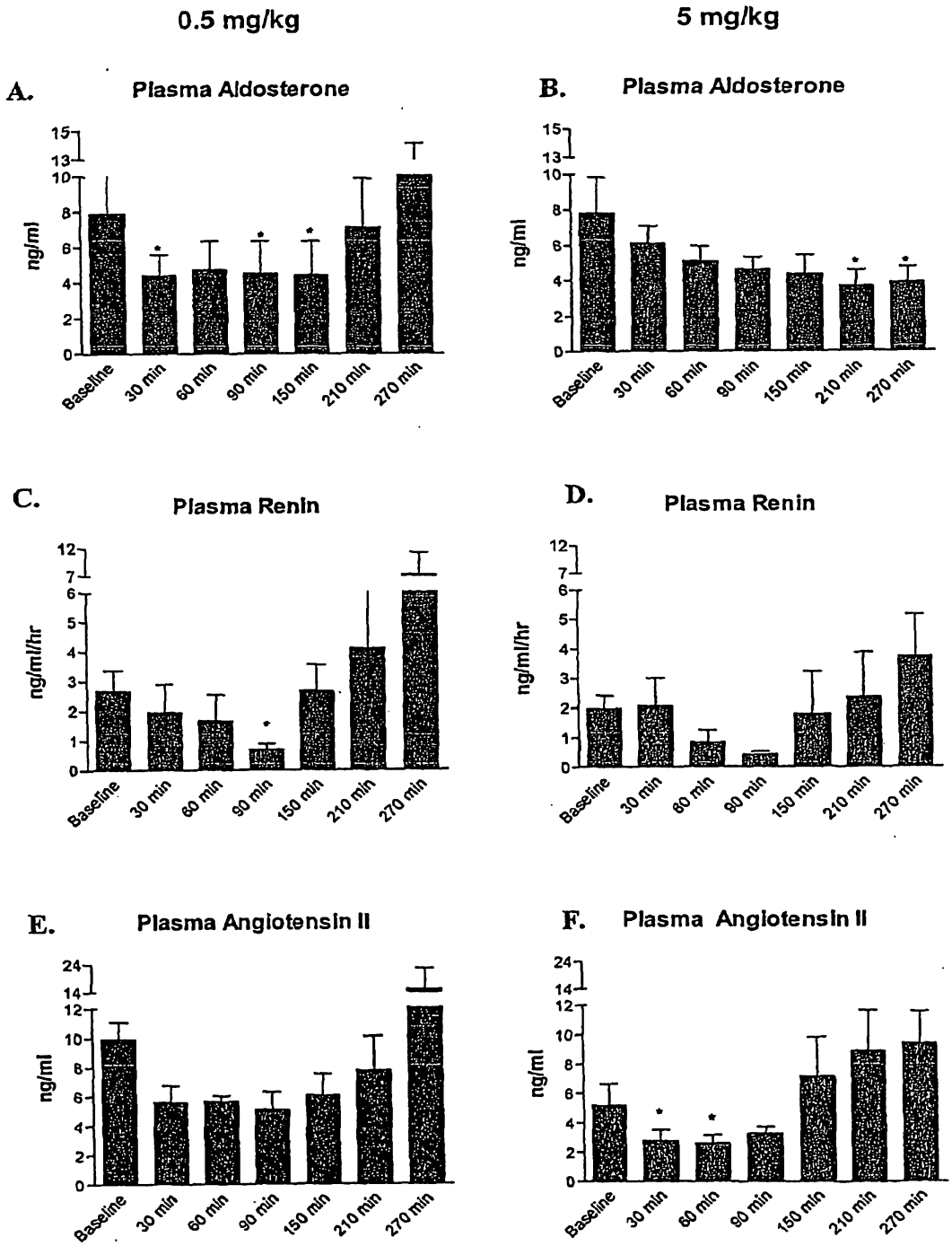

0.5 mg/kg
5 mg/kg
A.
Plasma Aldosterone
B.
Plasma Aldosterone
ng/ml
C.
Plasma Renin
D.
Plasma Renin
ng/ml/hr
E.
Plasma Angiotensin II
F.
Plasma Angiotensin II
ng/ml
Baseline
30 min
60 min
90 min
150 min
210 min
270 min

Figure 17

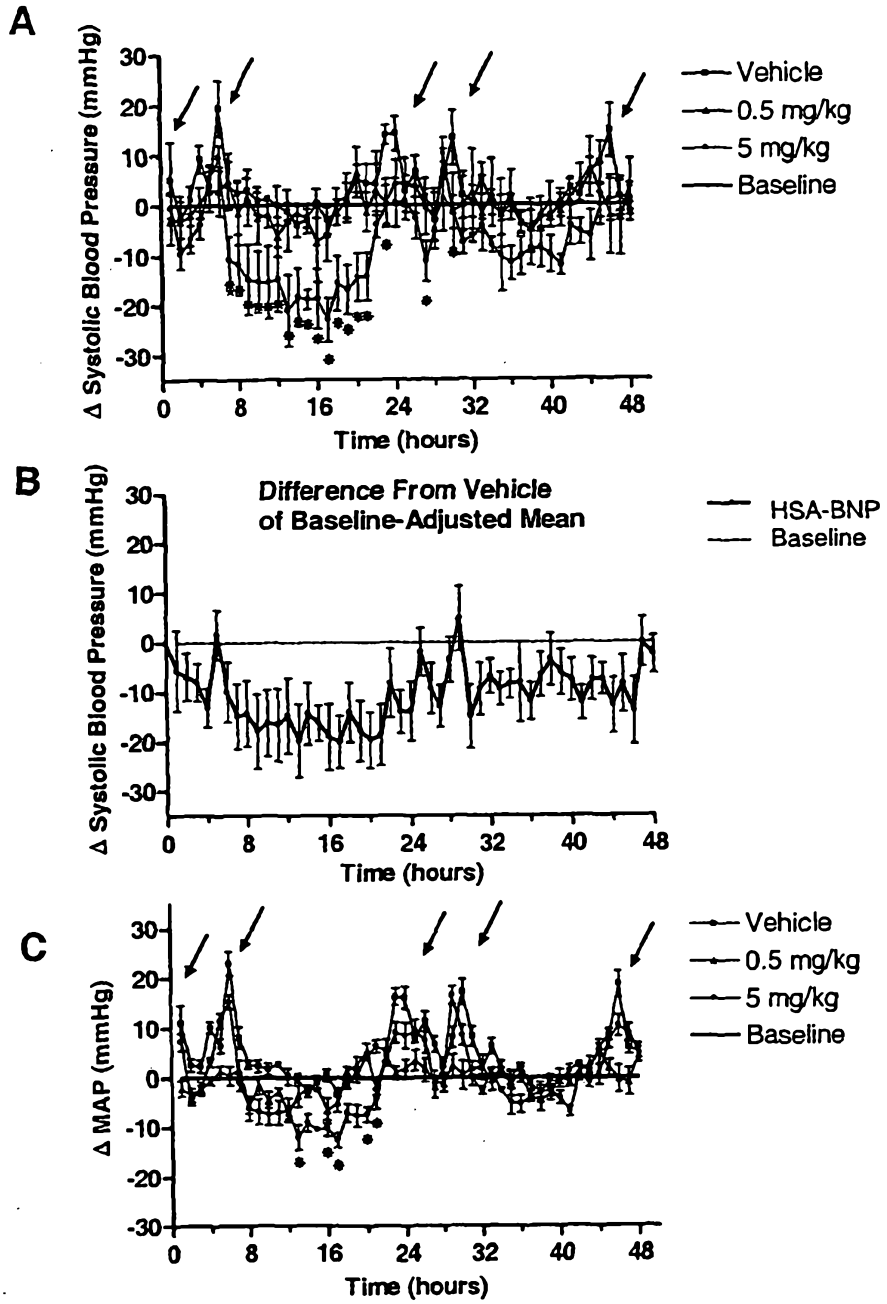
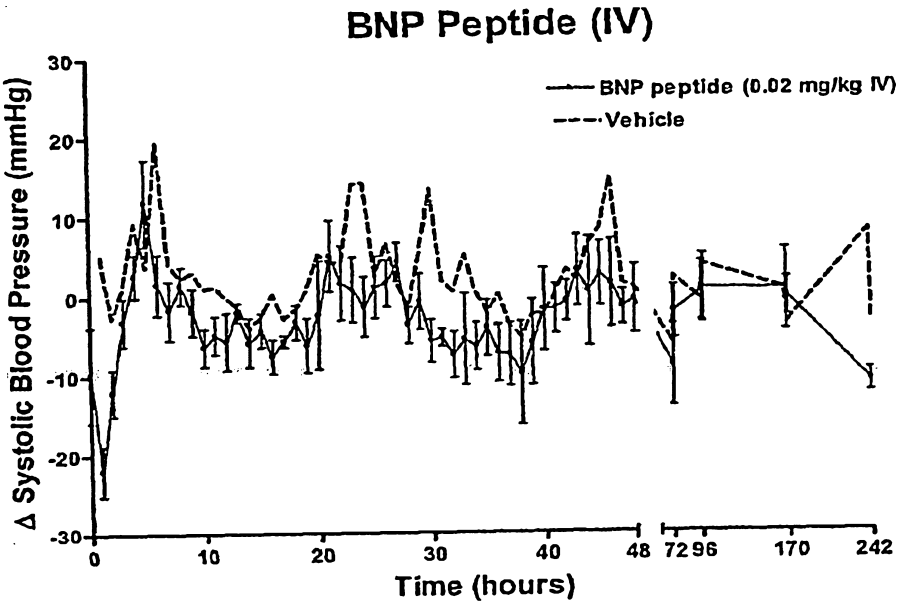

A
Δ Systolic Blood Pressure (mmHg)
30
20
10
0
-10
-20
-30
0
8
16
24
32
40
48
Time (hours)
Vehicle
0.5 mg/kg
5 mg/kg
Baseline
B
Difference From Vehicle
of Baseline-Adjusted Mean
Δ Systolic Blood Pressure (mmHg)
Time (hours)
HSA-BNP
Baseline
C
Δ MAP (mmHg)
Time (hours)
Vehicle
0.5 mg/kg
5 mg/kg
Baseline

**Figure 18**

A.


BNP Peptide (IV)
BNP peptide (0.02 mg/kg IV)
Vehicle
Δ Systolic Blood Pressure (mmHg)
30
20
10
0
-10
-20
-30
0
10
20
30
40
48
72
96
170
242
Time (hours)

B.

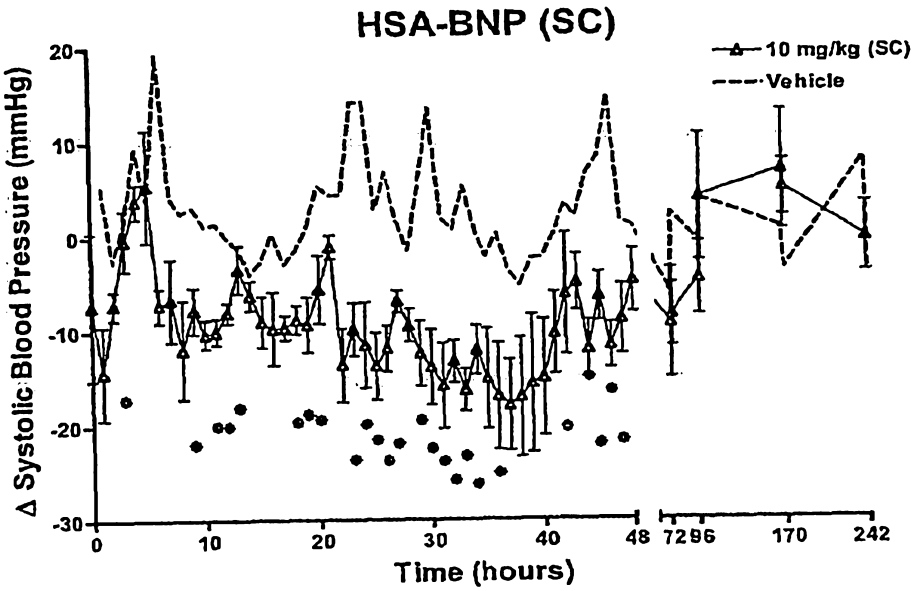

HSA-BNP (SC)
10 mg/kg (SC)
Vehicle
Δ Systolic Blood Pressure (mmHg)
20
10
0
-10
-20
-30
0
10
20
30
40
48
72
96
170
242
Time (hours)

Figure 19

**FIGURE 20**

```
   1  ATGCGCCCCACCTGGGCCTGGTGGCTGTTCCTGGTGCTGCTGCTGGCCCTGTGGGCCCCC 60
   1   M  R  P  T  W  A  W  W  L  F  L  V  L  L  L  A  L  W  A  P  20

  61  GCCCGCGGCGAAGATGACATCATAATTGCAACAAAGAATGGAAAAGTCAGAGGGATGAAC 120
  21   A  R  G  E  D  D  I  I  I  A  T  K  N  G  K  V  R  G  M  N  40

 121  TTGACAGTTTTTGGTGGCACGGTAACAGCCTTTCTTGGAATTCCCTATGCACAGCCACCT 180
  41   L  T  V  F  G  G  T  V  T  A  F  L  G  I  P  Y  A  Q  P  P  60

 181  CTTGGTAGACTTCGATTCAAAAAGCCACAGTCTCTGACCAAGTGGTCTGATATTTGGAAT 240
  61   L  G  R  L  R  F  K  K  P  Q  S  L  T  K  W  S  D  I  W  N  80

 241  GCCACAAAATATGCAAATTCTTGCTGTCAGAACATAGATCAAAGTTTTCCAGGCTTCCAT 300
  81   A  T  K  Y  A  N  S  C  C  Q  N  I  D  Q  S  F  P  G  F  H  100

 301  GGATCAGAGATGTGGAACCCAAACACTGACCTCAGTGAAGACTGTTTATATCTAAATGTA 360
 101   G  S  E  M  W  N  P  N  T  D  L  S  E  D  C  L  Y  L  N  V  120

 361  TGGATTCCAGCACCTAAACCAAAAAATGCCACTGTATTGATATGGATTTATGGTGGTGGT 420
 121   W  I  P  A  P  K  P  K  N  A  T  V  L  I  W  I  Y  G  G  G  140

 421  TTTCAAACTGGAACATCATCTTTACATGTTTATGATGGCAAGTTTCTGGCTCGGGTTGAA 480
 141   F  Q  T  G  T  S  S  L  H  V  Y  D  G  K  F  L  A  R  V  E  160

 481  AGAGTTATTGTAGTGTCAATGAACTATAGGGTGGGTGCCCTAGGATTCTTAGCTTTGCCA 540
 161   R  V  I  V  V  S  M  N  Y  R  V  G  A  L  G  F  L  A  L  P  180

 541  GGAAATCCTGAGGCTCCAGGGAACATGGGTTTATTTGATCAACAGTTGGCTCTTCAGTGG 600
 181   G  N  P  E  A  P  G  N  M  G  L  F  D  Q  Q  L  A  L  Q  W  200

 601  GTTCAAAAAAATATAGCAGCCTTTGGTGGAAATCCTAAAAGTGTAACTCTCTTTGGAGAA 660
 201   V  Q  K  N  I  A  A  F  G  G  N  P  K  S  V  T  L  F  G  E  220

 661  AGTTCAGGAGCAGCTTCAGTTAGCCTGCATTTGCTTTCTCCTGGAAGCCATTCATTGTTC 720
 221   S  S  G  A  A  S  V  S  L  H  L  L  S  P  G  S  H  S  L  F  240

 721  ACCAGAGCCATTCTGCAAAGTGGATCCTTTAATGCTCCTTGGGCGGTAACATCTCTTTAT 780
 241   T  R  A  I  L  Q  S  G  S  F  N  A  P  W  A  V  T  S  L  Y  260

 781  GAAGCTAGGAACAGAACGTTGAACTTAGCTAAATTGACTGGTTGCTCTAGAGAGAATGAG 840
 261   E  A  R  N  R  T  L  N  L  A  K  L  T  G  C  S  R  E  N  E  280

 841  ACTGAAATAATCAAGTGTCTTAGAAATAAAGATCCCCAAGAAATTCTTCTGAATGAAGCA 900
 281   T  E  I  I  K  C  L  R  N  K  D  P  Q  E  I  L  L  N  E  A  300

 901  TTTGTTGTCCCCTATGGGACTCCTTTGGGAGTAAACTTTGGTCCGACCGTGGATGGTGAT 960
 301   F  V  V  P  Y  G  T  P  L  G  V  N  F  G  P  T  V  D  G  D  320

 961  TTTCTCACTGACATGCCAGACATATTACTTGAACTTGGACAATTTAAAAAAACCCAGATT 1020
 321   F  L  T  D  M  P  D  I  L  L  E  L  G  Q  F  K  K  T  Q  I  340

1021  TTGGTGGGTGTTAATAAAGATGAAGGGACATGGTTTTTAGTCGGTGGTGCTCCTGGCTTC 1080
 341   L  V  G  V  N  K  D  E  G  T  W  F  L  V  G  G  A  P  G  F  360

1081  AGCAAAGATAACAATAGTATCATAACTAGAAAAGAATTTCAGGAAGGTTTAAAAATATTT 1140
 361   S  K  D  N  N  S  I  I  T  R  K  E  F  Q  E  G  L  K  I  F  380

1141  TTTCCAGGAGTGAGTGAGTTTGGAAAGGAATCCATCCTTTTTCATTACACAGACTGGGTA 1200
 381   F  P  G  V  S  E  F  G  K  E  S  I  L  F  H  Y  T  D  W  V  400

1201  GATGATCAGAGACCTGAAAACTACCGTGAGGCCTTGGGTGATGTTGTTGGGGATTATAAT 1260
 401   D  D  Q  R  P  E  N  Y  R  E  A  L  G  D  V  V  G  D  Y  N  420

1261  TTCATATGCCCTGCCTTGGAGTTCACCAAGAAGTTCTCAGAATGGGGAAATAATGCCTTT 1320
 421   F  I  C  P  A  L  E  F  T  K  K  F  S  E  W  G  N  N  A  F  440

1321  TTCTACTATTTTGAACACCGATCCTCCAAACTTCCGTGGCCAGAATGGATGGGAGTGATG 1380
 441   F  Y  Y  F  E  H  R  S  S  K  L  P  W  P  E  W  M  G  V  M  460

1381  CATGGCTATGAAATTGAATTTGTCTTTGGTTTACCTCTGGAAAGAAGAGATAATTACACA 1440
 461   H  G  Y  E  I  E  F  V  F  G  L  P  L  E  R  R  D  N  Y  T  480

1441  AAAGCCGAGGAAATTTTGAGTAGATCCATAGTGAAACGGTGGGCAAATTTTGCAAAATAT 1500
```

```
 481   K  A  E  E  I  L  S  R  S  I  V  K  R  W  A  N  F  A  K  Y  500

1501  GGGAATCCAAATGAGACTCAGAACAATAGCACAAGCTGGCCTGTCTTCAAAAGCACTGAA 1560
 501   G  N  P  N  E  T  Q  N  N  S  T  S  W  P  V  F  K  S  T  E  520

1561  CAAAAATATCTAACCTTGAATACAGAGTCAACAAGAATAATGACGAAACTACGTGCTCAA 1620
 521   Q  K  Y  L  T  L  N  T  E  S  T  R  I  M  T  K  L  R  A  Q  540

1621  CAATGTCGATTCTGGACATCATTTTTTCCAAAAGTCGATGCACACAAGAGTGAGGTTGCT 1680
 541   Q  C  R  F  W  T  S  F  F  P  K  V  D  A  H  K  S  E  V  A  560

1681  CATCGATTTAAAGATTTGGGAGAAGAAAATTTCAAAGCCTTGGTGTTGATTGCCTTTGCT 1740
 561   H  R  F  K  D  L  G  E  E  N  F  K  A  L  V  L  I  A  F  A  580

1741  CAGTATCTTCAGCAGTGTCCATTTGAAGATCATGTAAAATTAGTGAATGAAGTAACTGAA 1800
 581   Q  Y  L  Q  Q  C  P  F  E  D  H  V  K  L  V  N  E  V  T  E  600

1801  TTTGCAAAAACATGTGTTGCTGATGAGTCAGCTGAAAATTGTGACAAATCACTTCATACC 1860
 601   F  A  K  T  C  V  A  D  E  S  A  E  N  C  D  K  S  L  H  T  620

1861  CTTTTTGGAGACAAATTATGCACAGTTGCAACTCTTCGTGAAACCTATGGTGAAATGGCT 1920
 621   L  F  G  D  K  L  C  T  V  A  T  L  R  E  T  Y  G  E  M  A  640

1921  GACTGCTGTGCAAAACAAGAACCTGAGAGAAATGAATGCTTCTTGCAACACAAAGATGAC 1980
 641   D  C  C  A  K  Q  E  P  E  R  N  E  C  F  L  Q  H  K  D  D  660

1981  AACCCAAACCTCCCCCGATTGGTGAGACCAGAGGTTGATGTGATGTGCACTGCTTTTCAT 2040
 661   N  P  N  L  P  R  L  V  R  P  E  V  D  V  M  C  T  A  F  H  680

2041  GACAATGAAGAGACATTTTTGAAAAAATACTTATATGAAATTGCCAGAAGACATCCTTAC 2100
 681   D  N  E  E  T  F  L  K  K  Y  L  Y  E  I  A  R  R  H  P  Y  700

2101  TTTTATGCCCCGGAACTCCTTTTCTTTGCTAAAAGGTATAAAGCTGCTTTTACAGAATGT 2160
 701   F  Y  A  P  E  L  L  F  F  A  K  R  Y  K  A  A  F  T  E  C  720

2161  TGCCAAGCTGCTGATAAAGCTGCCTGCCTGTTGCCAAAGCTCGATGAACTTCGGGATGAA 2220
 721   C  Q  A  A  D  K  A  A  C  L  L  P  K  L  D  E  L  R  D  E  740

2221  GGGAAGGCTTCGTCTGCCAAACAGAGACTCAAGTGTGCCAGTCTCCAAAAATTTGGAGAA 2280
 741   G  K  A  S  S  A  K  Q  R  L  K  C  A  S  L  Q  K  F  G  E  760

2281  AGAGCTTTCAAAGCATGGGCAGTAGCTCGCCTGAGCCAGAGATTTCCCAAAGCTGAGTTT 2340
 761   R  A  F  K  A  W  A  V  A  R  L  S  Q  R  F  P  K  A  E  F  780

2341  GCAGAAGTTTCCAAGTTAGTGACAGATCTTACCAAAGTCCACACGGAATGCTGCCATGGA 2400
 781   A  E  V  S  K  L  V  T  D  L  T  K  V  H  T  E  C  C  H  G  800

2401  GATCTGCTTGAATGTGCTGATGACAGGGCGGACCTTGCCAAGTATATCTGTGAAAATCAA 2460
 801   D  L  L  E  C  A  D  D  R  A  D  L  A  K  Y  I  C  E  N  Q  820

2461  GATTCGATCTCCAGTAAACTGAAGGAATGCTGTGAAAAACCTCTGTTGGAAAAATCCCAC 2520
 821   D  S  I  S  S  K  L  K  E  C  C  E  K  P  L  L  E  K  S  H  840

2521  TGCATTGCCGAAGTGGAAAATGATGAGATGCCTGCTGACTTGCCTTCATTAGCTGCTGAT 2580
 841   C  I  A  E  V  E  N  D  E  M  P  A  D  L  P  S  L  A  A  D  860

2581  TTTGTTGAAAGTAAGGATGTTTGCAAAAACTATGCTGAGGCAAAGGATGTCTTCCTGGGC 2640
 861   F  V  E  S  K  D  V  C  K  N  Y  A  E  A  K  D  V  F  L  G  880

2641  ATGTTTTTGTATGAATATGCAAGAAGGCATCCTGATTACTCTGTCGTGCTGCTGCTGAGA 2700
 881   M  F  L  Y  E  Y  A  R  R  H  P  D  Y  S  V  V  L  L  L  R  900

2701  CTTGCCAAGACATATGAAACCACTCTAGAGAAGTGCTGTGCCGCTGCAGATCCTCATGAA 2760
 901   L  A  K  T  Y  E  T  T  L  E  K  C  C  A  A  A  D  P  H  E  920

2761  TGCTATGCCAAAGTGTTCGATGAATTTAAACCTCTTGTGGAAGAGCCTCAGAATTTAATC 2820
 921   C  Y  A  K  V  F  D  E  F  K  P  L  V  E  E  P  Q  N  L  I  940

2821  AAACAAAATTGTGAGCTTTTTGAGCAGCTTGGAGAGTACAAATTCCAGAATGCGCTATTA 2880
 941   K  Q  N  C  E  L  F  E  Q  L  G  E  Y  K  F  Q  N  A  L  L  960

2881  GTTCGTTACACCAAGAAAGTACCCCAAGTGTCAACTCCAACTCTTGTAGAGGTCTCAAGA 2940
 961   V  R  Y  T  K  K  V  P  Q  V  S  T  P  T  L  V  E  V  S  R  980

2941  AACCTAGGAAAAGTGGGCAGCAAATGTTGTAAACATCCTGAAGCAAAAAGAATGCCCTGT 3000
 981   N  L  G  K  V  G  S  K  C  C  K  H  P  E  A  K  R  M  P  C  1000
```

```
3001  GCAGAAGACTATCTATCCGTGGTCCTGAACCAGTTATGTGTGTTGCATGAGAAAACGCCA 3060
1001   A  E  D  Y  L  S  V  V  L  N  Q  L  C  V  L  H  E  K  T  P  1020

3061  GTAAGTGACAGAGTCACCAAATGCTGCACAGAATCCTTGGTGAACAGGCGACCATGCTTT 3120
1021   V  S  D  R  V  T  K  C  C  T  E  S  L  V  N  R  R  P  C  F  1040

3121  TCAGCTCTGGAAGTCGATGAAACATACGTTCCCAAAGAGTTTAATGCTGAAACATTCACC 3180
1041   S  A  L  E  V  D  E  T  Y  V  P  K  E  F  N  A  E  T  F  T  1060

3181  TTCCATGCAGATATATGCACACTTTCTGAGAAGGAGAGACAAATCAAGAAACAAACTGCA 3240
1061   F  H  A  D  I  C  T  L  S  E  K  E  R  Q  I  K  K  Q  T  A  1080

3241  CTTGTTGAGCTCGTGAAACACAAGCCCAAGGCAACAAAAGAGCAACTGAAAGCTGTTATG 3300
1081   L  V  E  L  V  K  H  K  P  K  A  T  K  E  Q  L  K  A  V  M  1100

3301  GATGATTTCGCAGCTTTTGTAGAGAAGTGCTGCAAGGCTGACGATAAGGAGACCTGCTTT 3360
1101   D  D  F  A  A  F  V  E  K  C  C  K  A  D  D  K  E  T  C  F  1120

3361  GCCGAGGAGGGTAAAAAACTTGTTGCTGCAAGTCAAGCTGCCTTAGGCTTATAA 3414
1121   A  E  E  G  K  K  L  V  A  A  S  Q  A  A  L  G  L  *  1138
```

FIGURE 21

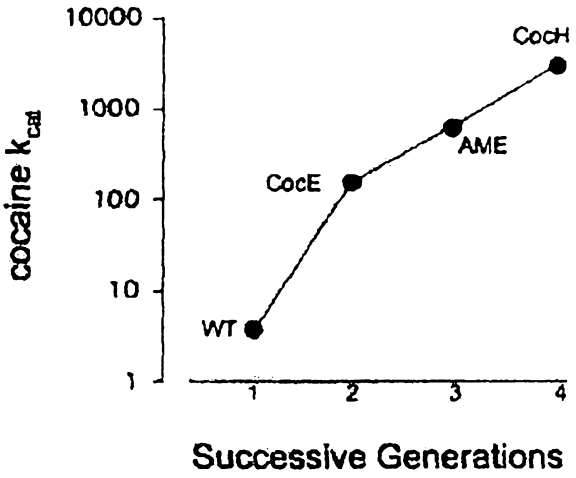

10000
1000
100
10
1
cocaine $k_{cat}$
WT
CocE
AME
CocH
1
2
3
4
Successive Generations

**FIGURE 22**

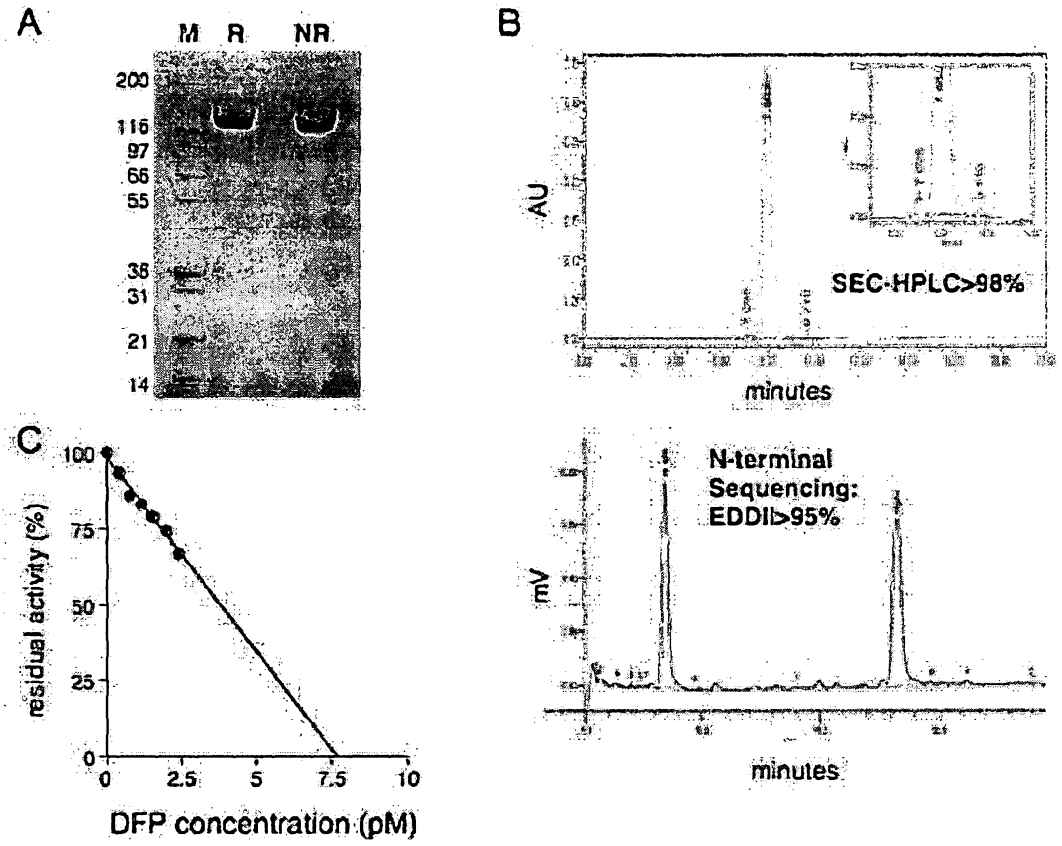

A
M
R
NR
200
116
97
66
55
36
31
21
14
B
AU
SEC-HPLC>98%
minutes
C
residual activity (%)
100
75
50
25
0
0
2.5
5
7.5
10
DFP concentration (pM)
N-terminal
Sequencing:
EDDI>95%
mV
minutes

FIGURE 23

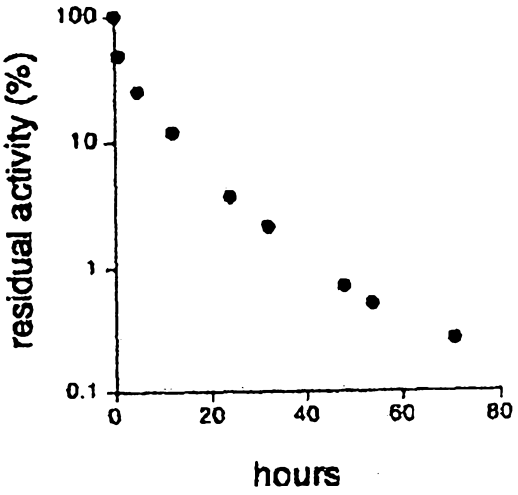


**FIGURE 24**

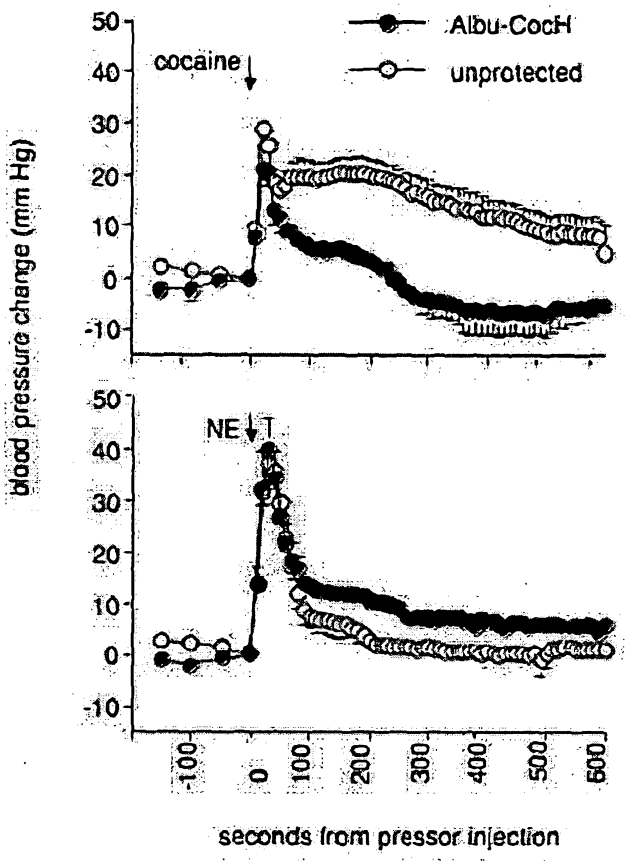

Albu-CocH
unprotected
cocaine
NE
T
blood pressure change (mm Hg)
seconds from pressor injection
50
40
30
20
10
0
-10
-100
0
100
200
300
400
500
600

**FIGURE 25**

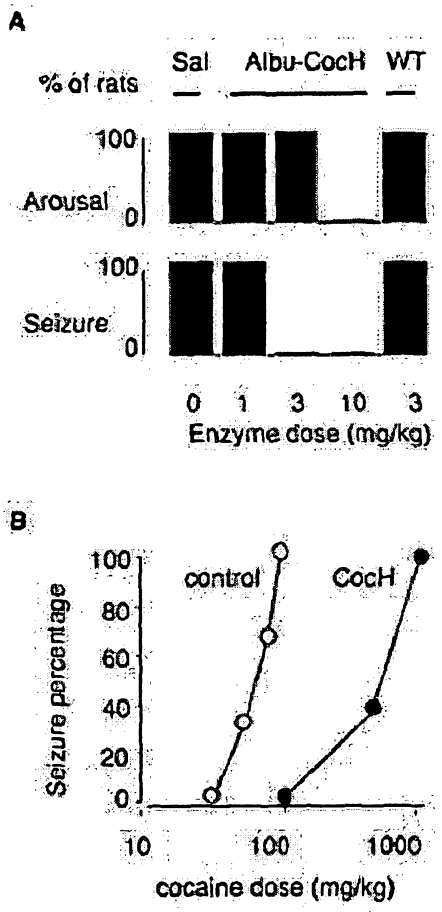
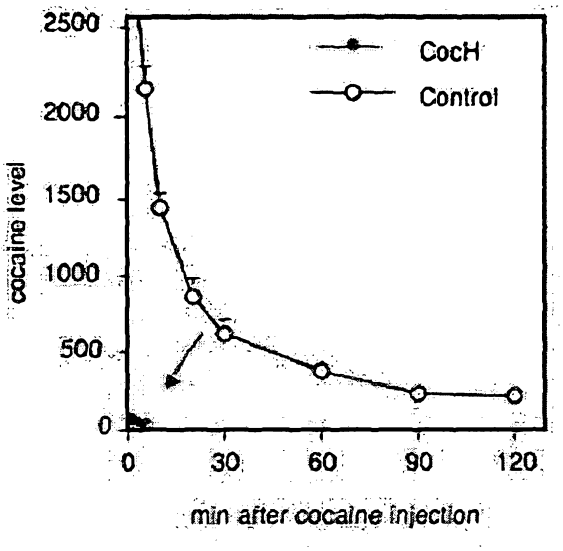

A
% of rats
Sal
Albu-CocH
WT
100
Arousal
0
100
Seizure
0
0 1 3 10 3
Enzyme dose (mg/kg)
B
Seizure percentage
100
80
60
40
20
0
control
CocH
10
100
1000
cocaine dose (mg/kg)

**FIGURE 26**


2500
2000
1500
1000
500
0
cocaine level
0
30
60
90
120
min after cocaine injection
CocH
Control

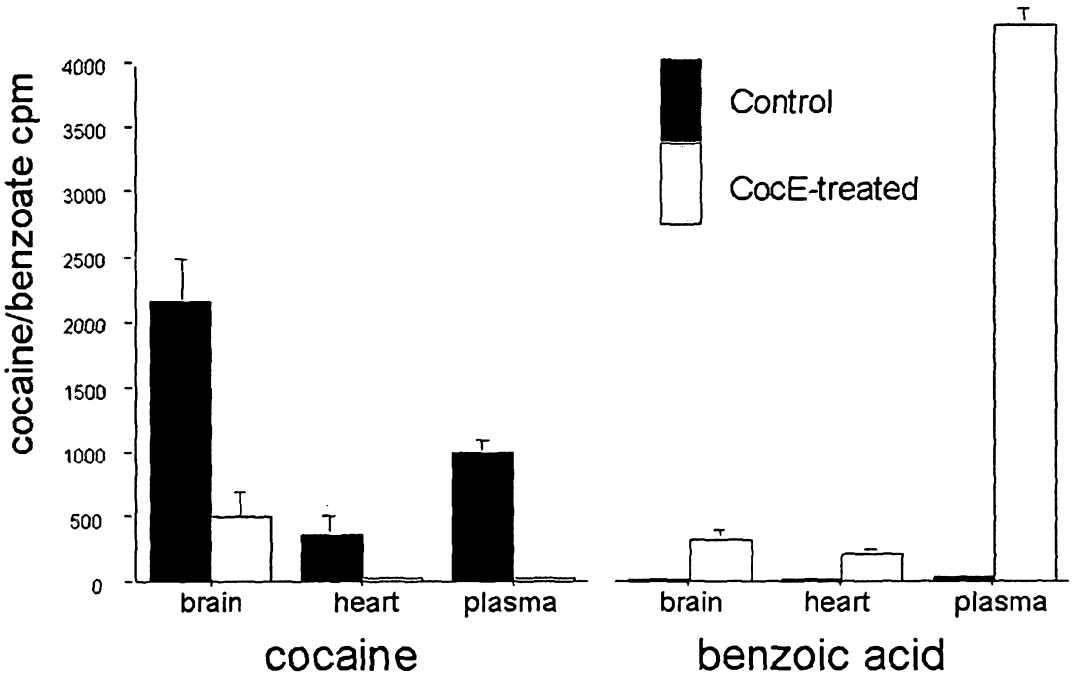
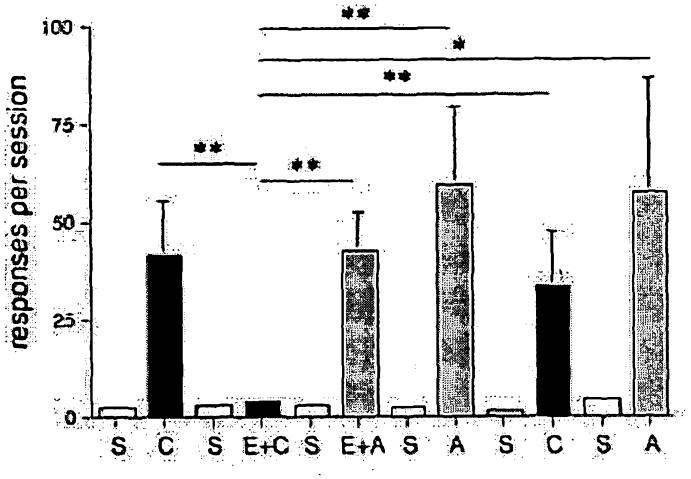

cocaine/benzoate cpm
4000
3500
3000
2500
2000
1500
1000
500
0
Control
CocE-treated
brain
heart
plasma
brain
heart
plasma
cocaine
benzoic acid

**Figure 27**

**FIGURE 28**



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<150> 60/423,623
<151> 2002-11-05

<160> 784

<170> PatentIn version 3.5

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35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His

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Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
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Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
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Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
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Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
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Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
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Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
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Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
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Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
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Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
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Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
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aaattagtga atgaagtaac tgaatttgca aaaacatgtg ttgctgatga gtcagctgaa 180

aattgtgaca aatcacttca tacccttttt ggagacaaat tatgcacagt tgcaactctt 240

cgtgaaacct atggtgaaat ggctgactgc tgtgcaaaac aagaacctga gagaaatgaa 300

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gaaattgcca gaagacatcc ttacttttat gccccggaac tccttttctt tgctaaaagg 480

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agacaaatca agaaacaaac tgcacttgtt gagcttgtga aacacaagcc caaggcaaca 1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag 1680

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<213> Homo sapiens

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His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
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Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
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His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

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145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
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Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
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Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240
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            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
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Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
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Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
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Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
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Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
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Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

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Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
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Leu

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tggtggttgg caaatgacta attaagttag tcaaggcgcc atcctcatga aaactgtgta 180

acataataac cgaagtgtcg aaaaggtggc accttgtcca attgaacacg ctcgatgaaa 240

aaaataagat atatataagg ttaagtaaag cgtctgttag aaaggaagtt tttccttttt 300

cttgctctct tgtcttttca tctactattt ccttcgtgta atacagggtc gtcagataca 360

tagatacaat tctattaccc ccatccatac aatg 394

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Leu Gly Ser Gln Ala
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Ala

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<400> 8

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Tyr Ser Arg Gly Val Phe Arg Arg
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1 5 10 15

Tyr Ser

<210> 10
<211> 18
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1 5 10 15

Tyr Ser

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<212> PRT
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20 25 30

Gln Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp
35 40 45

Phe Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu

50 55 60

Leu Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly
65 70 75 80

Val Ser Leu Xaa Lys Arg
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Tyr Ser Arg Ser Leu Glu Lys Arg
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Tyr Ser Arg Ser Leu Asp Lys Arg
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Ser Leu Asp Lys Arg
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<210> 16
<211> 19
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<400> 16

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
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Val His Ser

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<211> 29
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<213> Homo sapiens

<400> 17

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Leu Gly Gly Leu Ala Leu Leu Ala Ala Gly Val Asp Ala
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<211> 22
<212> PRT
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Ser Gly Gln Val Leu Gly
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Gly Pro Ser Leu Gly
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Tyr Ser Arg Gly Val Phe Arg Arg
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Ser Gly

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Ser Gly

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<400> 33

Met Lys Leu Ala Tyr Ser Leu Leu Leu Pro Leu Ala Gly Val Ser Ala
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Ser Val Ile Asn Tyr Lys Arg
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20 25 30

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Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Lys
50 55 60

Arg
65

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<211> 70
<212> PRT
<213> Homo sapiens

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1 5 10 15

Ser Gln Val Leu Gly Gln Pro Ile Asp Asp Thr Glu Ser Gln Thr Thr
20 25 30

Ser Val Asn Leu Met Ala Asp Asp Thr Glu Ser Ala Phe Ala Thr Gln
35 40 45

Thr Asn Ser Gly Gly Leu Asp Val Val Gly Leu Ile Ser Met Ala Glu
50 55 60

Glu Gly Glu Pro Lys Arg
65 70

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<210> 37
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<210> 38
<211> 24
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<220>
<223> primer used in generation XhoI and ClaI site in pPPC0006

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<210> 40
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<223> Synthetic oligonucleotide used to alter restriction sites in pPPC0007

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<213> Artificial Sequence

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<222> (40)..(40)
<223> n equals a,t,g, or c

<220>
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<222> (41)..(41)
<223> n equals a,t,g, or c

<220>
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<222> (42)..(42)
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<220>
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<223> n equals a,t,g, or c

<220>
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<222> (49)..(49)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (50)..(50)

<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (51)..(51)
<223> n equals a,t,g, or c

<400> 43
gcgcgcgttt aaacggccgg ccggcgcgcc ttattannnn nnnnnnnnnn n 51

<210> 44
<211> 4
<212> PRT
<213> Homo sapiens

<400> 44

Leu Asp Lys Arg
1

<210> 45
<211> 4
<212> PRT
<213> Homo sapiens

<400> 45

Leu Glu Lys Arg
1

<210> 46
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer useful for generation of albumin fusion protein in which the albumin moiety is c-terminal of the Therapeutic Protein

<220>
<221> misc_feature
<222> (19)..(19)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (20)..(20)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (21)..(21)
<223> n equals a,t,g, or c

<220>
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<222> (22)..(22)
<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

<220>
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<222> (25)..(25)
<223> n equals a,t,g, or c

<220>
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<223> n equals a,t,g, or c

<220>
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<222> (27)..(27)
<223> n equals a,t,g, or c

<220>
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<222> (28)..(28)
<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<222> (30)..(30)
<223> n equals a,t,g, or c

<220>
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<222> (31)..(31)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (32)..(32)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (33)..(33)
<223> n equals a,t,g, or c

<400> 46
aggagcgtcg acaaaagann nnnnnnnnnn nnn 33

<210> 47
<211> 52
<212> DNA

<213> Artificial Sequence

<220>
<223> reverse primer useful for generation of albumin fusion protein in which the albumin moiety is c-terminal of the Therapeutic Protein

<220>
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<222> (38)..(38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)..(39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (40)..(40)
<223> n equals a,t,g, or c

<220>
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<222> (41)..(41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (42)..(42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)..(43)
<223> n equals a,t,g, or c

<220>
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<222> (44)..(44)
<223> n equals a,t,g, or c

<220>
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<222> (45)..(45)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)..(46)
<223> n equals a,t,g, or c

<220>
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<222> (47)..(47)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (48)..(48)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (49)..(49)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (50)..(50)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (51)..(51)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (52)..(52)
<223> n equals a,t,g, or c

<400> 47
ctttaaatcg atgagcaacc tcactcttgt gtgcatcnnn nnnnnnnnnn nn 52

<210> 48
<211> 9
<212> PRT
<213> Homo sapiens

<400> 48

Asp Ala His Lys Ser Glu Val Ala His
1 5

<210> 49
<211> 11
<212> DNA
<213> Artificial Sequence

<220>
<223> Kozak sequence

<220>
<221> misc_feature
<222> (1)..(11)
<223> Kozak sequence

<400> 49
ccgccaccat g 11

<210> 50
<211> 46
<212> DNA
<213> Artificial Sequence

<220>
<223> forward primer useful for inserting Therapeutic protein into pC4:HSA vector

<220>
<221> misc_feature
<222> (29)..(29)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (30)..(30)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (31)..(31)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (32)..(32)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (33)..(33)
<223> n equals a,t,g, or c

<220>
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<222> (34)..(34)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (35)..(35)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (36)..(36)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (37)..(37)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (38)..(38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)..(39)
<223> n equals a,t,g, or c

<220>
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<222> (40)..(40)
<223> n equals a,t,g, or c

<220>
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<222> (41)..(41)

<223> n equals a,t,g, or c

<220>
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<222> (42)..(42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)..(43)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (44)..(44)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (45)..(45)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (46)..(46)
<223> n equals a,t,g, or c

<400> 50
ccgccgctcg aggggtgtgt ttcgtcgann nnnnnnnnnn nnnnnn 46

<210> 51
<211> 55
<212> DNA
<213> Artificial Sequence

<220>
<223> reverse primer useful for inserting Therapeutic protein into pC4:HSA vector

<220>
<221> misc_feature
<222> (38)..(38)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (39)..(39)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (40)..(40)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (41)..(41)
<223> n equals a,t,g, or c

<220>
<221> misc_feature

<222> (42)..(42)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (43)..(43)
<223> n equals a,t,g, or c

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<222> (44)..(44)
<223> n equals a,t,g, or c

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<222> (45)..(45)
<223> n equals a,t,g, or c

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<222> (46)..(46)
<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<222> (48)..(48)
<223> n equals a,t,g, or c

<220>
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<222> (49)..(49)
<223> n equals a,t,g, or c

<220>
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<222> (50)..(50)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (51)..(51)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (52)..(52)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (53)..(53)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (54)..(54)
<223> n equals a,t,g, or c

<220>
<221> misc_feature
<222> (55)..(55)
<223> n equals a,t,g, or c

<400> 51
agtcccatcg atgagcaacc tcactcttgt gtgcatcnnn nnnnnnnnnn nnnnn 55

<210> 52
<211> 733
<212> DNA
<213> Homo sapiens

<400> 52
gggatccgga gcccaaatct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg 60

aattcgaggg tgcaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga 120

tctcccggac tcctgaggtc acatgcgtgg tggtggacgt aagccacgaa gaccctgagg 180

tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg 240

aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact 300

ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca acccccatcg 360

agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc 420

catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct 480

atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga 540

ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag ctcaccgtgg 600

acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc 660

acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc 720

gactctagag gat 733

<210> 53
<211> 5
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa equals any of the twenty naturally ocurring L-amino acids

<400> 53

Trp Ser Xaa Trp Ser
1 5

<210> 54
<211> 86
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic sequence with 4 tandem copies of the GAS binding site found in the IRF1 promoter (Rothman et al., Immunity 1:457-468 (1994)), 18 nucleotides complementary to the SV40 early promoter, and a Xho I restriction site.

<400> 54
gcgcctcgag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc 60

cccgaaatat ctgccatctc aattag 86

<210> 55
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic sequence complementary to the SV40 promter; includes a Hind III restriction site.

<400> 55
gcggcaagct ttttgcaaag cctaggc 27

<210> 56
<211> 271
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic promoter for use in biological assays; includes GAS binding sites found in the IRF1 promoter

<400> 56
ctcgagattt ccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg 60

aaatatctgc catctcaatt agtcagcaac catagtcccg cccctaactc cgcccatccc 120

gcccctaact ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat 180

ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt 240

ttttggaggc ctaggctttt gcaaaaagct t 271

<210> 57
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence; includes a Xho I restriction site.

<400> 57
gcgctcgagg gatgacagcg atagaacccc gg 32

<210> 58
<211> 31
<212> DNA

<213> Artificial Sequence

<220>
<223> Synthetic primer complementary to human genomic EGR-1 promoter sequence; includes a Hind III restriction site.

<400> 58
gcgaagcttc gcgactcccc ggatccgcct c 31

<210> 59
<211> 12
<212> DNA
<213> Homo sapiens

<400> 59
ggggactttc cc 12

<210> 60
<211> 73
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic primer with 4 tandem copies of the NF-KB binding site (GGGGACTTTCCC), 18 nucleotides complementary to the 5' end of the SV40 early promoter sequence, and a XhoI restriction site.

<400> 60
gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg 60

ccatctcaat tag 73

<210> 61
<211> 256
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic promoter for use in biological assays; includes NF-KB binding sites.

<400> 61
ctcgagggga ctttcccggg gactttccgg ggactttccg ggactttcca tctgccatct 60

caattagtca gcaaccatag tcccgcccct aactccgccc atcccgcccc taactccgcc 120

cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga 180

ggccgcctcg gcctctgagc tattccagaa gtagtgagga ggctttttg gaggcctagg 240

cttttgcaaa aagctt 256

<210> 62
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH

domains

<400> 62
caggtgcagc tggtgcagtc tgg 23

<210> 63
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 63
caggtcaact taagggagtc tgg 23

<210> 64
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 64
gaggtgcagc tggtggagtc tgg 23

<210> 65
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 65
caggtgcagc tgcaggagtc ggg 23

<210> 66
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 66
gaggtgcagc tgttgcagtc tgc 23

<210> 67
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate VH forward primer useful for amplifying human VH domains

<400> 67
caggtacagc tgcagcagtc agg 23

<210> 68
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 68
tgaggagacg gtgaccaggg tgcc 24

<210> 69
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 69
tgaagagacg gtgaccattg tccc 24

<210> 70
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 70
tgaggagacg gtgaccaggg ttcc 24

<210> 71
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate JH reverse primer useful for amplifying human VH domains

<400> 71
tgaggagacg gtgaccgtgg tccc 24

<210> 72
<211> 23
<212> DNA

<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 72
gacatccaga tgacccagtc tcc 23

<210> 73
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 73
gatgttgtga tgactcagtc tcc 23

<210> 74
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 74
gatattgtga tgactcagtc tcc 23

<210> 75
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 75
gaaattgtgt tgacgcagtc tcc 23

<210> 76
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 76
gacatcgtga tgacccagtc tcc 23

<210> 77

<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 77
gaaacgacac tcacgcagtc tcc 23

<210> 78
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vkappa forward primer useful for amplifying human VL domains

<400> 78
gaaattgtgc tgactcagtc tcc 23

<210> 79
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 79
cagtctgtgt tgacgcagcc gcc 23

<210> 80
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 80
cagtctgccc tgactcagcc tgc 23

<210> 81
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 81
tcctatgtgc tgactcagcc acc 23

<210> 82
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 82
tcttctgagc tgactcagga ccc 23

<210> 83
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 83
cacgttatac tgactcaacc gcc 23

<210> 84
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 84
caggctgtgc tcactcagcc gtc 23

<210> 85
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Vlambda forward primer useful for amplifying human VL domains

<400> 85
aattttatgc tgactcagcc cca 23

<210> 86
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 86

acgtttgatt tccaccttgg tccc 24

<210> 87
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 87
acgtttgatc tccagcttgg tccc 24

<210> 88
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jkappa reverse primer useful for amplifying human VL domains

<400> 88
acgtttgata tccactttgg tccc 24

<210> 89
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 89
acgtttgatc tccaccttgg tccc 24

<210> 90
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<400> 90
acgtttaatc tccagtcgtg tccc 24

<210> 91
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 91
cagtctgtgt tgacgcagcc gcc 23

<210> 92
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 92
cagtctgccc tgactcagcc tgc 23

<210> 93
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 93
tcctatgtgc tgactcagcc acc 23

<210> 94
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 94
tcttctgagc tgactcagga ccc 23

<210> 95
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 95
cacgttatac tgactcaacc gcc 23

<210> 96
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 96
caggctgtgc tcactcagcc gtc 23

<210> 97
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Degenerate Jlambda reverse primer useful for amplifying human VL domains

<400> 97
aattttatgc tgactcagcc cca 23

<210> 98
<211> 5
<212> PRT
<213> Homo sapiens

<400> 98

Cys Asp Leu Pro Gln
1 5

<210> 99
<211> 165
<212> PRT
<213> Homo sapiens

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> Xaa equals Arg or Lys

<220>
<221> MISC_FEATURE
<222> (113)..(113)
<223> Xaa equals Ala or Val

<400> 99

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp Leu
65 70 75 80

Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Xaa Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 100
<211> 165
<212> PRT
<213> Homo sapiens

<220>
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<222> (23)..(23)
<223> Xaa equals Arg or Lys

<220>
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<222> (113)..(113)
<223> Xaa equals Ala or Val

<400> 100

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met Asn
100 105 110

Xaa Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 101
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<223> Xaa equals Arg or Lys

<400> 101

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
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Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Met Glu

85 90 95

Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met Asn
100 105 110

Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu Arg
145 150 155 160

Leu Arg Arg Lys Glu
165

<210> 102
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<223> Xaa equals Arg or Lys

<220>
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<223> Xaa equals Ser or Val

<220>
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<223> Xaa equals Cys or Leu

<220>
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<223> Xaa equals Val or Cys

<220>
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<223> Xaa equals Met or Asp

<400> 102

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Xaa Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

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Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Xaa Xaa Xaa Xaa Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met Tyr
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys Arg
145                 150                 155                 160

Leu Lys Ser Lys Glu
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<210>  103
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<213>  Homo sapiens


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<223>  Xaa equals Ala or Val

<400>  103

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Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
            20                  25                  30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
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50 55 60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ala Ala Trp Asp Glu
65 70 75 80

Asp Leu Leu Asp Lys Phe Cys Thr Glu Leu Tyr Gln Gln Leu Asn Asp
85 90 95

Leu Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu
100 105 110

Met Asn Xaa Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile
115 120 125

Thr Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val
130 135 140

Val Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln
145 150 155 160

Glu Arg Leu Arg Arg Lys Glu
165

<210> 104
<211> 166
<212> PRT
<213> Homo sapiens

<400> 104

Met Cys Asp Leu Pro Glu Thr His Ser Leu Asp Asn Arg Arg Thr Leu
1 5 10 15

Met Leu Leu Ala Gln Met Ser Arg Ile Ser Pro Ser Ser Cys Leu Met
20 25 30

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln
35 40 45

Phe Gln Lys Ala Pro Ala Ile Ser Val Leu His Glu Leu Ile Gln Gln
50 55 60

Ile Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ser Thr Gly Trp Asn
65 70 75 80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
85 90 95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr

100 105 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
115 120 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
130 135 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145 150 155 160

Thr Gly Tyr Leu Arg Asn
165

<210> 105
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic signal peptide

<400> 105

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
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Leu Trp Ala Pro Ala Arg Gly
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<210> 106

<400> 106
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<210> 107
<211> 106
<212> DNA
<213> Artificial sequence

<220>
<223> primer for full-length IFNb amplification, has BamHI cloning site

<400> 107
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tgtgcttctc cactacagct ctttccatga gctacaactt gcttgg 106

<210> 108
<211> 55
<212> DNA
<213> Artificial sequence

<220>
<223> primer for full-length IFNb amplification, has ClaI cloning site

<400> 108
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcgtt tcggaggtaa cctgt 55

<210> 109
<211> 41
<212> DNA
<213> Homo sapiens

<400> 109
cgcgcgcgtc gacaaaagat gtgatctgcc tcaaacccac a 41

<210> 110
<211> 59
<212> DNA
<213> Homo sapiens

<400> 110
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 111
<211> 21
<212> PRT
<213> Homo sapiens

<400> 111

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala
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<210> 112
<211> 24
<212> PRT
<213> Homo sapiens

<400> 112

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg
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<210> 113
<211> 1497
<212> DNA
<213> Hypocrea jecorina

<400> 113
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attagcatga aaggctatga gaaattctgg agacggcttg ttgaatcatg gcgttccatt 180

cttcgacaag caaagcgttc cgtcgcagta gcaggcactc attcccgaaa aaactcggag 240

attcctaagt agcgatggaa ccggaataat ataataggca atacattgag ttgcctcgac 300

ggttgcaatg caggggtact gagcttggac ataactgttc cgtaccccac ctcttctcaa 360

cctttggcgt ttccctgatt cagcgtaccc gtacaagtcg taatcactat taacccagac 420

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ctgcttgacc gactggggct gttcgaagcc cgaatgtagg attgttatcc gaactctgct 540

cgtagaggca tgttgtgaat ctgtgtcggg caggacacgc ctcgaaggtt cacggcaagg 600

gaaaccaccg atagcagtgt ctagtagcaa cctgtaaagc cgcaatgcag catcactgga 660

aaatacaaac caatggctaa aagtacataa gttaatgcct aaagaagtca tataccagcg 720

gctaataatt gtacaatcaa gtggctaaac gtaccgtaat ttgccaacgg cttgtggggt 780

tgcagaagca acggcaaagc cccacttccc cacgtttgtt tcttcactca gtccaatctc 840

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taagaatgtc tgactcggag cgttttgcat acaaccaagg gcagtgatgg aagacagtga 960

aatgttgaca ttcaaggagt atttagccag ggatgcttga gtgtatcgtg taaggaggtt 1020

tgtctgccga tacgacgaat actgtatagt cacttctggt gaagtggtcc atattgaaat 1080

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gccactgcat ggtttcgaat agaaagagaa gcttagccaa gaacaatagc cgataaagat 1320

agcctcatta aacggaatga gctagtaggc aaagtcagcg aatgtgtata tataaaggtt 1380

cgaggtccgt gcctccctca tgctctcccc atctactcat caactcagat cctccaggag 1440

acttgtacac catcttttga ggcacagaaa cccaatagtc aaccgcggac tggcatc 1497

<210> 114
<211> 366
<212> DNA
<213> Aspergillus nidulans

<400> 114
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ttcctaccat ttatgtccta tcgttcaggg tcctatttgg accgctagaa atagactctg 120

ctcgatttgt ttccattatt cacgcaatta cgatagtatt tggctctttt cgtttggccc 180

aggtcaattc gggtaagacg cgatcacgcc attgtggccg ccggcgttgt gctgctgcta 240

ttccccgcat ataaacaacc cctccaccag ttcgttgggc tttgcgaatg ctgtactcta 300

tttcaagttg tcaaaagaga ggattcaaaa aattataccc cagatatcaa agatatcaaa 360

gccatc 366

<210> 115
<211> 1646
<212> DNA
<213> Hypocrea jecorina

<400> 115
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cgaagctgct gcgaacccgg agaatcgaga tgtgctggaa agcttctagc gagcggctaa 120

attagcatga aaggctatga gaaattctgg agacggcttg ttgaatcatg gcgttccatt 180

cttcgacaag caaagcgttc cgtcgcagta gcaggcactc attcccgaaa aaactcggag 240

attcctaagt agcgatggaa ccggaataat ataataggca atacattgag ttgcctcgac 300

ggttgcaatg caggggtact gagcttggac ataactgttc cgtaccccac ctcttctcaa 360

cctttggcgt ttccctgatt cagcgtaccc gtacaagtcg taatcactat taacccagac 420

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cgtagaggca tgttgtgaat ctgtgtcggg caggacacgc ctcgaaggtt cacggcaagg 600

gaaaccaccg atagcagtgt ctagtagcaa cctgtaaagc cgcaatgcag catcactgga 660

aaatacaaac caatggctaa aagtacataa gttaatgcct aaagaagtca tataccagcg 720

gctaataatt gtacaatcaa gtggctaaac gtaccgtaat ttgccaacgg cttgtggggt 780

tgcagaagca acggcaaagc cccacttccc cacgtttgtt tcttcactca gtccaatctc 840

agctggtgat cccccaattg ggtcgcttgt ttgttccggt gaagtgaaag aagacagagg 900

taagaatgtc tgactcggag cgttttgcat acaaccaagg gcagtgatgg aagacagtga 960

aatgttgaca ttcaaggagt atttagccag ggatgcttga gtgtatcgtg taaggaggtt 1020

tgtctgccga tacgacgaat actgtatagt cacttctggt gaagtggtcc atattgaaat 1080

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aagtcagcga atgtgtatat ataaaggttc gaggtccgtg cctccctcat gctctcccca 1560

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<210> 116
<211> 516
<212> DNA
<213> Aspergillus nidulans

<400> 116
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aggtcaattc gggtaagacg cgatcacgcc attgtggccg ccggcgctgc agcctcttat 240

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cagacacgct cgacttcctg tcttcctatt gattgcagct tccaatttcg tcacacaaca 360

aggtcctacg ccggcgttgt gctgctgcta ttccccgcat ataaacaacc cctccaccag 420

ttcgttgggc tttgcgaatg ctgtactcta tttcaagttg tcaaaagaga ggattcaaaa 480

aattataccc cagatatcaa agatatcaaa gccatc 516

<210> 117
<211> 495
<212> DNA
<213> Homo sapiens

<400> 117
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atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120

gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300

caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

<210> 118
<211> 495
<212> DNA
<213> Homo sapiens

<400> 118
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atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120

gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300

caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

<210> 119
<211> 495
<212> DNA
<213> Homo sapiens

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atgaggagaa tctctctttt ctcctgcttg aaggacagac atgactttgg atttccccag 120

gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

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<211> 498
<212> DNA
<213> Homo sapiens

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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

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gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaataa 498

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<212> DNA
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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

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<212> DNA
<213> Homo sapiens

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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300

caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

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<212> DNA
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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

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<211> 495
<212> DNA
<213> Homo sapiens

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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

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gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaa 495

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<211> 495
<212> DNA
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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

ctagacaaat tctacactga actctaccag cagctgaatg acctggaagc ctgtgtgata 300

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tccagtggcc tgggctgcaa agtgctgagg cggcat 96

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<400> 141

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cagagcggac tgggctgtaa cagcttccgg tactga 456

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<211> 456
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aagaatttgc tggaccattt ggaagaaaag atgcctttag aagatgaggt cgtgccccca 180

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cagagcggac tgggctgtaa cagcttccgg tactga 456

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<211> 381
<212> DNA
<213> Homo sapiens

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tccgaagcca agcccggggc gccgccgaag gtcccgcgaa ccccgccggc agaggagctg 120

gccgagccgc aggctgcggg cggcggtcag aagaagggcg acaaggctcc cgggggcggg 180

ggcgccaatc tcaagggcga ccggtcgcga ctgctccggg acctgcgcgt ggacaccaag 240

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gccaacaaga agggcttgtc caagggctgc ttcggcctca agctggaccg aatcggctcc 360

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<211> 381
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<210> 151
<211> 96
<212> DNA
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tccagtggcc tgggctgcaa agtgctgagg cggcat 96

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<212> DNA
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<213> Homo sapiens

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acctacaaga tcccgcgtca gcggattatg gattactatg agaccaacag ccagtgctcc 180

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Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
35 40 45

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
50 55 60

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
65 70 75 80

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Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
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Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
            100                 105                 110

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
        115                 120                 125

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
    130                 135                 140

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
145                 150                 155                 160

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
                165                 170                 175

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
            180                 185                 190

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
        195                 200                 205

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
    210                 215                 220

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
225                 230                 235                 240

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
                245                 250                 255

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
            260                 265                 270

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
        275                 280                 285

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
    290                 295                 300

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
305                 310                 315                 320

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
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325 330 335

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
340 345 350

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
355 360 365

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
370 375 380

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
385 390 395 400

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
405 410 415

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
420 425 430

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
435 440 445

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
450 455 460

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
465 470 475 480

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
485 490 495

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
500 505 510

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
515 520 525

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
530 535 540

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
545 550 555 560

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
565 570 575

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Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
            580                 585                 590

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Cys Asp Leu Pro Gln Thr
        595                 600                 605

His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg
    610                 615                 620

Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe
625                 630                 635                 640

Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro
                645                 650                 655

Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys
            660                 665                 670

Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr
        675                 680                 685

Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly
    690                 695                 700

Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala
705                 710                 715                 720

Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys
                725                 730                 735

Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser
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Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
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<400>  193

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1               5                   10                  15

Ile Ser Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
            20                  25                  30
```

```
Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
        35                  40                  45

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
    50                  55                  60

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
65                  70                  75                  80

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
                85                  90                  95

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
            100                 105                 110

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
        115                 120                 125

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
    130                 135                 140

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
145                 150                 155                 160

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
                165                 170                 175

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
            180                 185                 190

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
        195                 200                 205

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
    210                 215                 220

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
225                 230                 235                 240

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
                245                 250                 255

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
            260                 265                 270

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
        275                 280                 285
```

```
Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
    290                 295                 300

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
305                 310                 315                 320

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
                325                 330                 335

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
            340                 345                 350

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
        355                 360                 365

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
    370                 375                 380

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
385                 390                 395                 400

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
                405                 410                 415

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
            420                 425                 430

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
        435                 440                 445

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
    450                 455                 460

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
465                 470                 475                 480

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
                485                 490                 495

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
            500                 505                 510

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
        515                 520                 525

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
    530                 535                 540
```

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
545 550 555 560

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
565 570 575

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
580 585 590

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Cys Asp Leu Pro
595 600 605

Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln
610 615 620

Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe
625 630 635 640

Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr
645 650 655

Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser
660 665 670

Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe
675 680 685

Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile
690 695 700

Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile
705 710 715 720

Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu
725 730 735

Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met
740 745 750

Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys
755 760 765

Glu

<210> 194

<211> 779
<212> PRT
<213> Homo sapiens

<400> 194

Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Asp Ala His
20 25 30

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
35 40 45

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
50 55 60

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
65 70 75 80

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
85 90 95

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
100 105 110

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
115 120 125

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
130 135 140

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
145 150 155 160

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
165 170 175

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
180 185 190

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
195 200 205

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
210 215 220

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe

225 230 235 240

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
245 250 255

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
260 265 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
275 280 285

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
290 295 300

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
305 310 315 320

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
325 330 335

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
340 345 350

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
355 360 365

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
370 375 380

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
385 390 395 400

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
405 410 415

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
420 425 430

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
435 440 445

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
450 455 460

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
465 470 475 480

```
Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
                485                 490                 495

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
            500                 505                 510

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
        515                 520                 525

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
    530                 535                 540

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
545                 550                 555                 560

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
                565                 570                 575

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
            580                 585                 590

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
        595                 600                 605

Gln Ala Ala Leu Gly Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly
    610                 615                 620

Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu
625                 630                 635                 640

Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu
                645                 650                 655

Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu
            660                 665                 670

Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala
        675                 680                 685

Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln
    690                 695                 700

Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr
705                 710                 715                 720

Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr
                725                 730                 735
```

Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys
740 745 750

Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser
755 760 765

Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu
770 775

<210> 195
<211> 774
<212> PRT
<213> Homo sapiens

<400> 195

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Cys Asp Leu Pro Gln Thr His Ser
20 25 30

Leu Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile
35 40 45

Ser Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln
50 55 60

Glu Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu
65 70 75 80

His Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser
85 90 95

Ser Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu
100 105 110

Tyr Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly
115 120 125

Val Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg
130 135 140

Lys Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser
145 150 155 160

Pro Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser
165 170 175

```
Leu Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His
            180                 185                 190

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
        195                 200                 205

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
    210                 215                 220

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
225                 230                 235                 240

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
                245                 250                 255

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
            260                 265                 270

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
        275                 280                 285

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
    290                 295                 300

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
305                 310                 315                 320

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
                325                 330                 335

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
            340                 345                 350

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
        355                 360                 365

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
    370                 375                 380

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
385                 390                 395                 400

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
                405                 410                 415

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
            420                 425                 430
```

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
435 440 445

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
450 455 460

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
465 470 475 480

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
485 490 495

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
500 505 510

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
515 520 525

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
530 535 540

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
545 550 555 560

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
565 570 575

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
580 585 590

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
595 600 605

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
610 615 620

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
625 630 635 640

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
645 650 655

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
660 665 670

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro

675 680 685

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
690 695 700

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
705 710 715 720

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
725 730 735

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
740 745 750

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
755 760 765

Gln Ala Ala Leu Gly Leu
770

<210> 196
<211> 769
<212> PRT
<213> Homo sapiens

<400> 196

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
20 25 30

Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys
35 40 45

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
50 55 60

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
65 70 75 80

Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
85 90 95

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
100 105 110

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro

```
        115                 120                 125

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
    130                 135                 140

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
145                 150                 155                 160

Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu
                165                 170                 175

Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu Val Ala
            180                 185                 190

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        195                 200                 205

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    210                 215                 220

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
225                 230                 235                 240

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                245                 250                 255

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            260                 265                 270

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        275                 280                 285

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    290                 295                 300

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
305                 310                 315                 320

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                325                 330                 335

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            340                 345                 350

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        355                 360                 365
```

```
Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    370                 375                 380

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
385                 390                 395                 400

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                405                 410                 415

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            420                 425                 430

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        435                 440                 445

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    450                 455                 460

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
465                 470                 475                 480

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                485                 490                 495

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            500                 505                 510

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        515                 520                 525

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    530                 535                 540

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
545                 550                 555                 560

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                565                 570                 575

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            580                 585                 590

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        595                 600                 605

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    610                 615                 620
```

```
Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
625                 630                 635                 640

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                645                 650                 655

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            660                 665                 670

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        675                 680                 685

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    690                 695                 700

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
705                 710                 715                 720

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                725                 730                 735

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            740                 745                 750

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        755                 760                 765

Leu
```

<210> 197
<211> 835
<212> PRT
<213> Homo sapiens

<400> 197

```
Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1               5                   10                  15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
            20                  25                  30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
        35                  40                  45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
    50                  55                  60
```

```
Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val
65                  70                  75                  80

Ser Leu Asp Lys Arg Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser
                85                  90                  95

Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe
            100                 105                 110

Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe
        115                 120                 125

Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met
    130                 135                 140

Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala
145                 150                 155                 160

Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln
                165                 170                 175

Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu
            180                 185                 190

Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe
        195                 200                 205

Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala
    210                 215                 220

Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr
225                 230                 235                 240

Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu
                245                 250                 255

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
            260                 265                 270

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
        275                 280                 285

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
    290                 295                 300

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
305                 310                 315                 320
```

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
325 330 335

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
340 345 350

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
355 360 365

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
370 375 380

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
385 390 395 400

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
405 410 415

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
420 425 430

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
435 440 445

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
450 455 460

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
465 470 475 480

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
485 490 495

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
500 505 510

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
515 520 525

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
530 535 540

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
545 550 555 560

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe

```
                565                 570                 575

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
            580                 585                 590

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
        595                 600                 605

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
    610                 615                 620

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
625                 630                 635                 640

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
                645                 650                 655

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
            660                 665                 670

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
        675                 680                 685

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
    690                 695                 700

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
705                 710                 715                 720

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
                725                 730                 735

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
            740                 745                 750

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
        755                 760                 765

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
    770                 775                 780

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
785                 790                 795                 800

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
                805                 810                 815
```

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
820 825 830

Leu Gly Leu
835

<210> 198
<211> 774
<212> PRT
<213> Homo sapiens

<400> 198

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

```
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

```
Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
            660                 665                 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
        675                 680                 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700
```

```
Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705                 710                 715                 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770
```

<210> 199
<211> 773
<212> PRT
<213> Homo sapiens

<400> 199

```
Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys
1               5                   10                  15

Lys Ser Ser Cys Ser Val Gly Cys Asp Leu Pro Gln Thr His Ser Leu
            20                  25                  30

Gly Ser Arg Arg Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser
        35                  40                  45

Leu Phe Ser Cys Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu
    50                  55                  60

Glu Phe Gly Asn Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His
65                  70                  75                  80

Glu Met Ile Gln Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser
                85                  90                  95

Ala Ala Trp Asp Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr
            100                 105                 110

Gln Gln Leu Asn Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val
        115                 120                 125

Thr Glu Thr Pro Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys
    130                 135                 140
```

```
Tyr Phe Gln Arg Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro
145                 150                 155                 160

Cys Ala Trp Glu Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu
                165                 170                 175

Ser Thr Asn Leu Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys
            180                 185                 190

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
        195                 200                 205

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
    210                 215                 220

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
225                 230                 235                 240

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
                245                 250                 255

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
            260                 265                 270

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
        275                 280                 285

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
    290                 295                 300

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
305                 310                 315                 320

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
                325                 330                 335

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
            340                 345                 350

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
        355                 360                 365

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
    370                 375                 380

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
```

385 390 395 400

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
405 410 415

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
420 425 430

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
435 440 445

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
450 455 460

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
465 470 475 480

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
485 490 495

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
500 505 510

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
515 520 525

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
530 535 540

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
545 550 555 560

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
565 570 575

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
580 585 590

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
595 600 605

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
610 615 620

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
625 630 635 640

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
645 650 655

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
660 665 670

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
675 680 685

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
690 695 700

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
705 710 715 720

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
725 730 735

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
740 745 750

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
755 760 765

Ala Ala Leu Gly Leu
770

<210> 200
<211> 769
<212> PRT
<213> Homo sapiens

<400> 200

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg
20 25 30

Thr Leu Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys
35 40 45

Leu Lys Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn
50 55 60

Gln Phe Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln
65 70 75 80

```
Gln Ile Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp
                85                  90                  95

Glu Thr Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn
            100                 105                 110

Asp Leu Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro
        115                 120                 125

Leu Met Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg
    130                 135                 140

Ile Thr Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu
145                 150                 155                 160

Val Val Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu
                165                 170                 175

Gln Glu Ser Leu Arg Ser Lys Glu Asp Ala His Lys Ser Glu Val Ala
            180                 185                 190

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        195                 200                 205

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    210                 215                 220

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
225                 230                 235                 240

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                245                 250                 255

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            260                 265                 270

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        275                 280                 285

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    290                 295                 300

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
305                 310                 315                 320

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                325                 330                 335
```

```
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            340                 345                 350

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        355                 360                 365

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    370                 375                 380

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
385                 390                 395                 400

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                405                 410                 415

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            420                 425                 430

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        435                 440                 445

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    450                 455                 460

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
465                 470                 475                 480

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                485                 490                 495

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            500                 505                 510

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        515                 520                 525

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    530                 535                 540

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
545                 550                 555                 560

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                565                 570                 575

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            580                 585                 590
```

```
Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        595                 600                 605

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    610                 615                 620

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
625                 630                 635                 640

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                645                 650                 655

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            660                 665                 670

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        675                 680                 685

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    690                 695                 700

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
705                 710                 715                 720

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                725                 730                 735

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            740                 745                 750

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        755                 760                 765

Leu
```

<210> 201
<211> 774
<212> PRT
<213> Homo sapiens

<400> 201

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30
```

```
His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
```

```
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525
```

```
Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
            660                 665                 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
        675                 680                 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705                 710                 715                 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770
```

<210> 202
<211> 774
<212> PRT
<213> Homo sapiens

<400> 202

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr

725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 203
<211> 638
<212> PRT
<213> Homo sapiens

<400> 203

Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met

```
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415
```

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 204
<211> 638
<212> PRT
<213> Homo sapiens

<400> 204

```
Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1               5                   10                  15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
            20                  25                  30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
        35                  40                  45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
    50                  55                  60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65                  70                  75                  80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
                85                  90                  95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
            100                 105                 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        115                 120                 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
    130                 135                 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145                 150                 155                 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255
```

```
Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485                 490                 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
            500                 505                 510
```

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 205
<211> 574
<212> PRT
<213> Homo sapiens

<400> 205

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
50 55 60

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
65 70 75 80

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
85 90 95

```
Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
            100                 105                 110

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
        115                 120                 125

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
    130                 135                 140

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
145                 150                 155                 160

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
                165                 170                 175

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
            180                 185                 190

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
        195                 200                 205

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
    210                 215                 220

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
225                 230                 235                 240

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
                245                 250                 255

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
            260                 265                 270

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
        275                 280                 285

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
    290                 295                 300

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
305                 310                 315                 320

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
                325                 330                 335

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
```

340 345 350

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
355 360 365

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
370 375 380

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
385 390 395 400

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
405 410 415

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
420 425 430

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
435 440 445

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
450 455 460

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
465 470 475 480

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
485 490 495

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
500 505 510

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
515 520 525

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
530 535 540

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
545 550 555 560

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
565 570

<210> 206
<211> 638
<212> PRT
<213> Homo sapiens

<400> 206

```
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1               5                   10                  15

Leu Gly Ser Gln Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
            20                  25                  30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
        35                  40                  45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
    50                  55                  60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65                  70                  75                  80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
                85                  90                  95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
            100                 105                 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        115                 120                 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
    130                 135                 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145                 150                 155                 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240
```

```
Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485                 490                 495
```

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 207
<211> 638
<212> PRT
<213> Homo sapiens

<400> 207

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

```
Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
                85                  90                  95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
            100                 105                 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        115                 120                 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
    130                 135                 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145                 150                 155                 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335
```

```
Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485                 490                 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
            500                 505                 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
        515                 520                 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
    530                 535                 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545                 550                 555                 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
                565                 570                 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
```

580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 208
<211> 640
<212> PRT
<213> Homo sapiens

<400> 208

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly Ser Pro Lys Met Val Gln Gly Ser Gly
20 25 30

Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly
35 40 45

Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His
50 55 60

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
65 70 75 80

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
85 90 95

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
100 105 110

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
115 120 125

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
130 135 140

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
145 150 155 160

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp

```
                165                 170                 175

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
            180                 185                 190

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
        195                 200                 205

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
    210                 215                 220

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
225                 230                 235                 240

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
                245                 250                 255

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
            260                 265                 270

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
        275                 280                 285

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
    290                 295                 300

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
305                 310                 315                 320

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
                325                 330                 335

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
            340                 345                 350

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
        355                 360                 365

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
    370                 375                 380

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
385                 390                 395                 400

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
                405                 410                 415
```

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
420 425 430

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
435 440 445

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
450 455 460

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
465 470 475 480

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
485 490 495

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
500 505 510

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
515 520 525

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
530 535 540

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
545 550 555 560

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
565 570 575

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
580 585 590

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
595 600 605

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
610 615 620

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635 640

<210> 209
<211> 640
<212> PRT
<213> Homo sapiens

<400> 209

```
Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1               5                   10                  15

Leu Trp Ala Pro Ala Arg Gly Ser Pro Lys Met Val Gln Gly Ser Gly
            20                  25                  30

Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly
        35                  40                  45

Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His
    50                  55                  60

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
65                  70                  75                  80

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
                85                  90                  95

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
            100                 105                 110

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
        115                 120                 125

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
    130                 135                 140

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
145                 150                 155                 160

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
                165                 170                 175

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
            180                 185                 190

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
        195                 200                 205

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
    210                 215                 220

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
225                 230                 235                 240

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
                245                 250                 255
```

```
Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
            260                 265                 270

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
        275                 280                 285

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
    290                 295                 300

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
305                 310                 315                 320

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
                325                 330                 335

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
            340                 345                 350

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
        355                 360                 365

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
    370                 375                 380

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
385                 390                 395                 400

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
                405                 410                 415

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
            420                 425                 430

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
        435                 440                 445

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
    450                 455                 460

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
465                 470                 475                 480

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
                485                 490                 495

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
            500                 505                 510
```

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
515 520 525

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
530 535 540

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
545 550 555 560

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
565 570 575

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
580 585 590

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
595 600 605

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
610 615 620

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635 640

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

<400> 210

Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Gly Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

```
Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
            100                 105                 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        115                 120                 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
    130                 135                 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145                 150                 155                 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
```

```
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485                 490                 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
            500                 505                 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
        515                 520                 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
    530                 535                 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545                 550                 555                 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
                565                 570                 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
            580                 585                 590
```

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 211
<211> 571
<212> PRT
<213> Homo sapiens

<400> 211

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
50 55 60

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
65 70 75 80

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
85 90 95

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
100 105 110

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
115 120 125

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
130 135 140

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
145 150 155 160

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
165 170 175

```
Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
            180                 185                 190

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
        195                 200                 205

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
    210                 215                 220

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
225                 230                 235                 240

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
                245                 250                 255

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
            260                 265                 270

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
        275                 280                 285

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
    290                 295                 300

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
305                 310                 315                 320

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
                325                 330                 335

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
            340                 345                 350

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
        355                 360                 365

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
    370                 375                 380

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
385                 390                 395                 400

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
                405                 410                 415

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
            420                 425                 430
```

```
Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
        435                 440                 445

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
    450                 455                 460

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
465                 470                 475                 480

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
                485                 490                 495

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
            500                 505                 510

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
        515                 520                 525

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
    530                 535                 540

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
545                 550                 555                 560

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                565                 570


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

<400>  212

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1               5                   10                  15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
            20                  25                  30

Gly Gly Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
        35                  40                  45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
    50                  55                  60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65                  70                  75                  80
```

```
Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
                85                  90                  95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
            100                 105                 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
        115                 120                 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
    130                 135                 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145                 150                 155                 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335
```

```
Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
                485                 490                 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
            500                 505                 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
        515                 520                 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
    530                 535                 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545                 550                 555                 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
                565                 570                 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
```

580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

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

<400> 213

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Gly Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
65 70 75 80

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met

```
                165                 170                 175

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
            180                 185                 190

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
        195                 200                 205

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415
```

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
420 425 430

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
435 440 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
450 455 460

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465 470 475 480

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
485 490 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
500 505 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
515 520 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
530 535 540

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
545 550 555 560

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
565 570 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
580 585 590

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
595 600 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
610 615 620

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 214
<211> 641
<212> PRT
<213> Homo sapiens

<400> 214

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255
```

```
Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510
```

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
610 615 620

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg
625 630 635 640

His

<210> 215
<211> 642
<212> PRT
<213> Homo sapiens

<400> 215

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Gly Gly Gly Asp Ala His Lys Ser Glu Val
50 55 60

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
65 70 75 80

```
Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
                85                  90                  95

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
            100                 105                 110

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
        115                 120                 125

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
    130                 135                 140

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
145                 150                 155                 160

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
                165                 170                 175

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
            180                 185                 190

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
        195                 200                 205

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
    210                 215                 220

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
225                 230                 235                 240

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
                245                 250                 255

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
            260                 265                 270

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
        275                 280                 285

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
    290                 295                 300

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
305                 310                 315                 320

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
```

325 330 335

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
340 345 350

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
355 360 365

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
370 375 380

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
385 390 395 400

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
405 410 415

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
420 425 430

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
435 440 445

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
450 455 460

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
465 470 475 480

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
485 490 495

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
500 505 510

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
515 520 525

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
530 535 540

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
545 550 555 560

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
565 570 575

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
580 585 590

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
595 600 605

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
610 615 620

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
625 630 635 640

Gly Leu

<210> 216
<211> 639
<212> PRT
<213> Homo sapiens

<400> 216

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asn Pro Met Tyr Asn Ala Val Ser
20 25 30

Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu Glu
35 40 45

Lys Met Pro Leu Glu Asp Asp Ala His Lys Ser Glu Val Ala His Arg
50 55 60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65 70 75 80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
85 90 95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
100 105 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
115 120 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
130 135 140

```
Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145                 150                 155                 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                325                 330                 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400
```

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
405 410 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
420 425 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
435 440 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
450 455 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465 470 475 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
485 490 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
500 505 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
515 520 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
530 535 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545 550 555 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
565 570 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
580 585 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
595 600 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
610 615 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 217
<211> 639

<212> PRT
<213> Homo sapiens

<400> 217

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                  10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240
```

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg

485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Asn Pro Met Tyr Asn Ala Val Ser Asn Ala Asp Leu Met Asp Phe
610 615 620

Lys Asn Leu Leu Asp His Leu Glu Glu Lys Met Pro Leu Glu Asp
625 630 635

<210> 218
<211> 646
<212> PRT
<213> Homo sapiens

<400> 218

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Val Val Pro Pro Gln Val Leu
20 25 30

Ser Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu
35 40 45

Val Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Ala His
50 55 60

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe

65 70 75 80

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
85 90 95

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
100 105 110

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
115 120 125

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
130 135 140

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
145 150 155 160

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
165 170 175

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
180 185 190

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
195 200 205

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
210 215 220

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
225 230 235 240

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
245 250 255

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
260 265 270

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
275 280 285

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
290 295 300

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
305 310 315 320

```
Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
                325                 330                 335

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
            340                 345                 350

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
        355                 360                 365

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
    370                 375                 380

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
385                 390                 395                 400

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
                405                 410                 415

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
            420                 425                 430

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
        435                 440                 445

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
    450                 455                 460

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
465                 470                 475                 480

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
                485                 490                 495

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
            500                 505                 510

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
        515                 520                 525

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
    530                 535                 540

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
545                 550                 555                 560

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
                565                 570                 575
```

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
580 585 590

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
595 600 605

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
610 615 620

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
625 630 635 640

Gln Ala Ala Leu Gly Leu
645

<210> 219
<211> 646
<212> PRT
<213> Homo sapiens

<400> 219

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

```
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400
```

```
Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Glu Val Val Pro Pro Gln Val Leu Ser Glu Pro Asn Glu Glu Ala
    610                 615                 620

Gly Ala Ala Leu Ser Pro Leu Pro Glu Val Pro Pro Trp Thr Gly Glu
625                 630                 635                 640

Val Ser Pro Ala Gln Arg
```

645

<210> 220
<211> 629
<212> PRT
<213> Homo sapiens

<400> 220

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Ser Asp Arg Ser Ala Leu Leu
20 25 30

Lys Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Asp Ala His Lys
35 40 45

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
50 55 60

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
65 70 75 80

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
85 90 95

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
100 105 110

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
115 120 125

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
130 135 140

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
145 150 155 160

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
165 170 175

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
180 185 190

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
195 200 205

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro

```
    210                 215                 220

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
225                 230                 235                 240

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
                245                 250                 255

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
            260                 265                 270

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
        275                 280                 285

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
    290                 295                 300

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
305                 310                 315                 320

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
                325                 330                 335

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
            340                 345                 350

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
        355                 360                 365

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
    370                 375                 380

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
385                 390                 395                 400

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
                405                 410                 415

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
            420                 425                 430

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
        435                 440                 445

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
    450                 455                 460
```

```
Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
465                 470                 475                 480

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
                485                 490                 495

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
            500                 505                 510

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
        515                 520                 525

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
    530                 535                 540

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
545                 550                 555                 560

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
                565                 570                 575

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
            580                 585                 590

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
        595                 600                 605

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
    610                 615                 620

Ala Ala Leu Gly Leu
625
```

<210> 221
<211> 629
<212> PRT
<213> Homo sapiens

<400> 221

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45
```

```
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300
```

```
Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560
```

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu
610 615 620

Leu Thr Ala Pro Arg
625

<210> 222
<211> 631
<212> PRT
<213> Homo sapiens

<400> 222

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Leu Ser Lys Gly Cys Phe Gly
20 25 30

Leu Lys Leu Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys Asp Ala
35 40 45

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
50 55 60

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
65 70 75 80

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
85 90 95

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
100 105 110

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
115 120 125

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
130 135 140

```
Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
145                 150                 155                 160

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
                165                 170                 175

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
            180                 185                 190

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
        195                 200                 205

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
    210                 215                 220

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
225                 230                 235                 240

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
                245                 250                 255

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
            260                 265                 270

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
        275                 280                 285

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
    290                 295                 300

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
305                 310                 315                 320

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
                325                 330                 335

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
            340                 345                 350

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
        355                 360                 365

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
    370                 375                 380

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
```

385 390 395 400

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
405 410 415

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
420 425 430

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
435 440 445

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
450 455 460

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
465 470 475 480

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
485 490 495

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
500 505 510

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
515 520 525

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
530 535 540

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
545 550 555 560

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
565 570 575

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
580 585 590

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
595 600 605

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
610 615 620

Ser Gln Ala Ala Leu Gly Leu
625 630

<210> 223
<211> 631
<212> PRT
<213> Homo sapiens

<400> 223

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

```
Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480
```

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Gly Leu Ser Lys Gly Cys Phe Gly Leu Lys Leu Asp Arg Ile Gly
610 615 620

Ser Met Ser Gly Leu Gly Cys
625 630

<210> 224
<211> 647
<212> PRT
<213> Homo sapiens

<400> 224

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Val Lys Tyr Asp Pro Cys Phe
20 25 30

Gly His Lys Ile Asp Arg Ile Asn His Val Ser Asn Leu Gly Cys Pro
35 40 45

Ser Leu Arg Asp Pro Arg Pro Asn Ala Pro Ser Thr Ser Ala Asp Ala
50 55 60

```
His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
65                  70                  75                  80

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
                85                  90                  95

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
            100                 105                 110

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
        115                 120                 125

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
    130                 135                 140

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
145                 150                 155                 160

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
                165                 170                 175

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
            180                 185                 190

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
        195                 200                 205

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
    210                 215                 220

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
225                 230                 235                 240

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
                245                 250                 255

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
            260                 265                 270

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
        275                 280                 285

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
    290                 295                 300

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
305                 310                 315                 320
```

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
325 330 335

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
340 345 350

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
355 360 365

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
370 375 380

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
385 390 395 400

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
405 410 415

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
420 425 430

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
435 440 445

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
450 455 460

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
465 470 475 480

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
485 490 495

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
500 505 510

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
515 520 525

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
530 535 540

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
545 550 555 560

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys

565 570 575

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
580 585 590

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
595 600 605

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
610 615 620

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
625 630 635 640

Ser Gln Ala Ala Leu Gly Leu
645

<210> 225
<211> 647
<212> PRT
<213> Homo sapiens

<400> 225

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val

```
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380
```

```
Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Glu Val Lys Tyr Asp Pro Cys Phe Gly His Lys Ile Asp Arg Ile
    610                 615                 620

Asn His Val Ser Asn Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro
625                 630                 635                 640
```

Asn Ala Pro Ser Thr Ser Ala
645

<210> 226
<211> 670
<212> PRT
<213> Homo sapiens

<400> 226

Met Trp Trp Arg Leu Trp Trp Leu Leu Leu Leu Leu Leu Leu Trp
1 5 10 15

Pro Met Val Trp Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe
50 55 60

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
65 70 75 80

Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe
85 90 95

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
100 105 110

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
115 120 125

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
130 135 140

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
145 150 155 160

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
165 170 175

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
180 185 190

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
195 200 205

```
Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
    210                 215                 220

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
225                 230                 235                 240

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
                245                 250                 255

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
            260                 265                 270

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
        275                 280                 285

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
    290                 295                 300

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
305                 310                 315                 320

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
                325                 330                 335

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
            340                 345                 350

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
        355                 360                 365

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
    370                 375                 380

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
385                 390                 395                 400

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
                405                 410                 415

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
            420                 425                 430

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
        435                 440                 445

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
    450                 455                 460
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```
Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
465                 470                 475                 480

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
                485                 490                 495

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
            500                 505                 510

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
        515                 520                 525

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
    530                 535                 540

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
545                 550                 555                 560

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
                565                 570                 575

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
            580                 585                 590

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
        595                 600                 605

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
    610                 615                 620

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
625                 630                 635                 640

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
                645                 650                 655

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665                 670

<210>  227
<211>  637
<212>  PRT
<213>  Homo sapiens

<400>  227

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15
```

```
Tyr Ser Arg Ser Leu Asp Lys Arg Ser Leu Arg Arg Ser Ser Cys Phe
            20                  25                  30

Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn
        35                  40                  45

Ser Phe Arg Tyr Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
    50                  55                  60

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
65                  70                  75                  80

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
                85                  90                  95

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
            100                 105                 110

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
        115                 120                 125

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
    130                 135                 140

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
145                 150                 155                 160

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
                165                 170                 175

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
            180                 185                 190

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
        195                 200                 205

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
    210                 215                 220

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
225                 230                 235                 240

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
                245                 250                 255

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
```

```
            260                 265                 270

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
        275                 280                 285

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
    290                 295                 300

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
305                 310                 315                 320

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
                325                 330                 335

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
            340                 345                 350

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
        355                 360                 365

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
    370                 375                 380

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
385                 390                 395                 400

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
                405                 410                 415

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
            420                 425                 430

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
        435                 440                 445

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
    450                 455                 460

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
465                 470                 475                 480

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
                485                 490                 495

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
            500                 505                 510
```

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
515 520 525

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
530 535 540

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
545 550 555 560

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
565 570 575

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
580 585 590

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
595 600 605

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
610 615 620

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 228
<211> 683
<212> PRT
<213> Homo sapiens

<400> 228

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Thr Lys Thr Glu Ser Ser Ser Arg
20 25 30

Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys
35 40 45

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
50 55 60

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
65 70 75 80

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
85 90 95

```
Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
            100                 105                 110

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
        115                 120                 125

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
    130                 135                 140

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
145                 150                 155                 160

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                165                 170                 175

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            180                 185                 190

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        195                 200                 205

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    210                 215                 220

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
225                 230                 235                 240

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                245                 250                 255

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            260                 265                 270

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        275                 280                 285

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    290                 295                 300

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
305                 310                 315                 320

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                325                 330                 335

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            340                 345                 350
```

```
Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        355                 360                 365

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    370                 375                 380

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
385                 390                 395                 400

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
                405                 410                 415

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
            420                 425                 430

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
        435                 440                 445

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
    450                 455                 460

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
465                 470                 475                 480

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
                485                 490                 495

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
            500                 505                 510

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
        515                 520                 525

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
    530                 535                 540

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
545                 550                 555                 560

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
                565                 570                 575

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
            580                 585                 590

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
        595                 600                 605
```

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
610 615 620

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
625 630 635 640

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
645 650 655

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
660 665 670

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 229
<211> 683
<212> PRT
<213> Homo sapiens

<400> 229

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Thr Lys Thr Glu Ser Ser Ser Arg
20 25 30

Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys
35 40 45

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
50 55 60

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
65 70 75 80

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
85 90 95

Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
100 105 110

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
115 120 125

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
130 135 140

```
Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
145                 150                 155                 160

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
                165                 170                 175

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
            180                 185                 190

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
        195                 200                 205

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
    210                 215                 220

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
225                 230                 235                 240

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
                245                 250                 255

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
            260                 265                 270

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
        275                 280                 285

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
    290                 295                 300

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
305                 310                 315                 320

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
                325                 330                 335

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
            340                 345                 350

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
        355                 360                 365

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
    370                 375                 380

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
```

385 390 395 400

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
405 410 415

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
420 425 430

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
435 440 445

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
450 455 460

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
465 470 475 480

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
485 490 495

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
500 505 510

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
515 520 525

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
530 535 540

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
545 550 555 560

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
565 570 575

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
580 585 590

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
595 600 605

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
610 615 620

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
625 630 635 640

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
645 650 655

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
660 665 670

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 230
<211> 675
<212> PRT
<213> Homo sapiens

<400> 230

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Pro Tyr His Pro Ser Glu Cys
20 25 30

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
35 40 45

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
50 55 60

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
65 70 75 80

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu
85 90 95

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
100 105 110

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
115 120 125

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
130 135 140

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
145 150 155 160

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
165 170 175

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
180 185 190

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
195 200 205

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
210 215 220

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
225 230 235 240

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
245 250 255

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
260 265 270

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
275 280 285

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
290 295 300

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
305 310 315 320

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
325 330 335

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
340 345 350

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
355 360 365

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
370 375 380

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
385 390 395 400

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
405 410 415

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
420 425 430

```
Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
        435                 440                 445

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
    450                 455                 460

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
465                 470                 475                 480

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
                485                 490                 495

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
            500                 505                 510

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
        515                 520                 525

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
    530                 535                 540

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
545                 550                 555                 560

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
                565                 570                 575

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
            580                 585                 590

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
        595                 600                 605

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
    610                 615                 620

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
625                 630                 635                 640

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
                645                 650                 655

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
            660                 665                 670

Leu Gly Leu
        675
```

<210> 231
<211> 675
<212> PRT
<213> Homo sapiens

<400> 231

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Pro Tyr His Pro Ser Glu Cys
20 25 30

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
35 40 45

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
50 55 60

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
65 70 75 80

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu
85 90 95

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
100 105 110

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
115 120 125

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
130 135 140

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
145 150 155 160

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
165 170 175

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
180 185 190

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
195 200 205

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
210 215 220

```
Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
225                 230                 235                 240

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
                245                 250                 255

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
            260                 265                 270

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
        275                 280                 285

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
    290                 295                 300

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
305                 310                 315                 320

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
                325                 330                 335

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
            340                 345                 350

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
        355                 360                 365

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
    370                 375                 380

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
385                 390                 395                 400

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
                405                 410                 415

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
            420                 425                 430

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
        435                 440                 445

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
    450                 455                 460

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
```

```
465                 470                 475                 480

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
                485                 490                 495

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
            500                 505                 510

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
        515                 520                 525

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
    530                 535                 540

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
545                 550                 555                 560

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
                565                 570                 575

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
            580                 585                 590

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
        595                 600                 605

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
    610                 615                 620

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
625                 630                 635                 640

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
                645                 650                 655

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
            660                 665                 670

Leu Gly Leu
        675


<210>  232
<211>  691
<212>  PRT
<213>  Homo sapiens

<400>  232

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
```

```
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Pro Tyr His Pro Ser Glu Cys
            20                  25                  30

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
        35                  40                  45

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
    50                  55                  60

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
65                  70                  75                  80

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Ser Gly Gly Gly Gly Ser
                85                  90                  95

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ala His Lys Ser Glu
            100                 105                 110

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
        115                 120                 125

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
    130                 135                 140

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
145                 150                 155                 160

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
                165                 170                 175

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
            180                 185                 190

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
        195                 200                 205

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
    210                 215                 220

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
225                 230                 235                 240

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
                245                 250                 255
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Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
            260                 265                 270

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
        275                 280                 285

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
    290                 295                 300

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
305                 310                 315                 320

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
                325                 330                 335

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
            340                 345                 350

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
        355                 360                 365

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
    370                 375                 380

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
385                 390                 395                 400

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
                405                 410                 415

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
            420                 425                 430

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
        435                 440                 445

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Lys Thr Thr Leu Glu
    450                 455                 460

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
465                 470                 475                 480

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
                485                 490                 495

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
            500                 505                 510
```

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
515 520 525

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
530 535 540

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
545 550 555 560

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
565 570 575

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
580 585 590

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
595 600 605

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
610 615 620

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
625 630 635 640

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
645 650 655

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
660 665 670

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
675 680 685

Leu Gly Leu
690

<210> 233
<211> 675
<212> PRT
<213> Homo sapiens

<400> 233

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Gly Pro Tyr His Pro Ser Glu Cys
20 25 30

```
Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
        35                  40                  45

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
    50                  55                  60

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
65                  70                  75                  80

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu
                85                  90                  95

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
            100                 105                 110

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
        115                 120                 125

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
    130                 135                 140

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
145                 150                 155                 160

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
                165                 170                 175

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
            180                 185                 190

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
        195                 200                 205

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
    210                 215                 220

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
225                 230                 235                 240

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
                245                 250                 255

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
            260                 265                 270

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
        275                 280                 285
```

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
290 295 300

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
305 310 315 320

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
325 330 335

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
340 345 350

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
355 360 365

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
370 375 380

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
385 390 395 400

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
405 410 415

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
420 425 430

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
435 440 445

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
450 455 460

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
465 470 475 480

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
485 490 495

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
500 505 510

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
515 520 525

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser

530 535 540

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
545 550 555 560

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
565 570 575

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
580 585 590

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
595 600 605

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
610 615 620

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
625 630 635 640

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
645 650 655

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
660 665 670

Leu Gly Leu
675

<210> 234
<211> 736
<212> PRT
<213> Homo sapiens

<400> 234

Met Arg Phe Pro Ser Ile Phe Thr Ala Val Leu Phe Ala Ala Ser Ser
1 5 10 15

Ala Leu Ala Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln
20 25 30

Ile Pro Ala Glu Ala Val Ile Gly Tyr Ser Asp Leu Glu Gly Asp Phe
35 40 45

Asp Val Ala Val Leu Pro Phe Ser Asn Ser Thr Asn Asn Gly Leu Leu
50 55 60

Phe Ile Asn Thr Thr Ile Ala Ser Ile Ala Ala Lys Glu Glu Gly Val

65 70 75 80

Ser Leu Asp Lys Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr
85 90 95

Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
100 105 110

Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg
115 120 125

Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr
130 135 140

Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His
145 150 155 160

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

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
180 185 190

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
195 200 205

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
210 215 220

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
225 230 235 240

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
245 250 255

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
260 265 270

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
275 280 285

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
290 295 300

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
305 310 315 320

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
325 330 335

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
340 345 350

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
355 360 365

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
370 375 380

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
385 390 395 400

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
405 410 415

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
420 425 430

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
435 440 445

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
450 455 460

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
465 470 475 480

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
485 490 495

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
500 505 510

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
515 520 525

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
530 535 540

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
545 550 555 560

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
565 570 575

```
Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
            580                 585                 590

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
        595                 600                 605

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
    610                 615                 620

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
625                 630                 635                 640

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
                645                 650                 655

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
            660                 665                 670

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
        675                 680                 685

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
    690                 695                 700

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
705                 710                 715                 720

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                725                 730                 735


<210>  235
<211>  669
<212>  PRT
<213>  Homo sapiens

<400>  235

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr
            20                  25                  30

Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser
        35                  40                  45

Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser
    50                  55                  60
```

```
Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp
65                  70                  75                  80

Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
                85                  90                  95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
            100                 105                 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320
```

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
325 330 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
340 345 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
355 360 365

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
370 375 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385 390 395 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
405 410 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
420 425 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
435 440 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
450 455 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465 470 475 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
485 490 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
500 505 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
515 520 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
530 535 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545 550 555 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu

565 570 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
580 585 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
595 600 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
610 615 620

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
625 630 635 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
645 650 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 236
<211> 670
<212> PRT
<213> Homo sapiens

<400> 236

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
20 25 30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
35 40 45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
50 55 60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65 70 75 80

Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe
85 90 95

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
100 105 110

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val

```
        115                 120                 125

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
    130                 135                 140

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
145                 150                 155                 160

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
                165                 170                 175

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
            180                 185                 190

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
        195                 200                 205

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
    210                 215                 220

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
225                 230                 235                 240

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
                245                 250                 255

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
            260                 265                 270

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
        275                 280                 285

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
    290                 295                 300

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
305                 310                 315                 320

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
                325                 330                 335

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
            340                 345                 350

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
        355                 360                 365
```

```
Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
    370                 375                 380

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
385                 390                 395                 400

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
                405                 410                 415

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
            420                 425                 430

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
        435                 440                 445

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
    450                 455                 460

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
465                 470                 475                 480

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
                485                 490                 495

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
            500                 505                 510

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
        515                 520                 525

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
    530                 535                 540

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
545                 550                 555                 560

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
                565                 570                 575

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
            580                 585                 590

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
        595                 600                 605

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
    610                 615                 620
```

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
625 630 635 640

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
645 650 655

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 237
<211> 682
<212> PRT
<213> Homo sapiens

<400> 237

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Lys Thr Glu Ser Ser Ser Arg Gly
20 25 30

Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile
35 40 45

Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser
50 55 60

Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr
65 70 75 80

Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu
85 90 95

Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
100 105 110

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
115 120 125

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
130 135 140

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
145 150 155 160

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
165 170 175

```
Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
            180                 185                 190

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
        195                 200                 205

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
    210                 215                 220

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
225                 230                 235                 240

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
                245                 250                 255

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
            260                 265                 270

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
        275                 280                 285

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
    290                 295                 300

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
305                 310                 315                 320

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
                325                 330                 335

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
            340                 345                 350

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
        355                 360                 365

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
    370                 375                 380

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
385                 390                 395                 400

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
                405                 410                 415

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
            420                 425                 430
```

```
Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
        435                 440                 445

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
    450                 455                 460

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
465                 470                 475                 480

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
                485                 490                 495

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
            500                 505                 510

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
        515                 520                 525

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
    530                 535                 540

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
545                 550                 555                 560

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
                565                 570                 575

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
            580                 585                 590

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
        595                 600                 605

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
    610                 615                 620

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
625                 630                 635                 640

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
                645                 650                 655

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
            660                 665                 670

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
```

675 680

<210> 238
<211> 681
<212> PRT
<213> Homo sapiens

<400> 238

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Thr Glu Ser Ser Ser Arg Gly Pro
20 25 30

Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro
35 40 45

Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys
50 55 60

Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn
65 70 75 80

Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90 95

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
100 105 110

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
115 120 125

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
130 135 140

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
145 150 155 160

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
165 170 175

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
180 185 190

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
195 200 205

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His

```
    210                 215                 220

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
225                 230                 235                 240

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
                245                 250                 255

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
            260                 265                 270

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
        275                 280                 285

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
    290                 295                 300

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
305                 310                 315                 320

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
                325                 330                 335

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
            340                 345                 350

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
        355                 360                 365

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
    370                 375                 380

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
385                 390                 395                 400

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
                405                 410                 415

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
            420                 425                 430

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
        435                 440                 445

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
    450                 455                 460
```

```
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
465                 470                 475                 480

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
                485                 490                 495

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
            500                 505                 510

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
        515                 520                 525

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
    530                 535                 540

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
545                 550                 555                 560

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
                565                 570                 575

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
            580                 585                 590

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
        595                 600                 605

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
    610                 615                 620

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
625                 630                 635                 640

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
                645                 650                 655

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
            660                 665                 670

Ala Ala Ser Gln Ala Ala Leu Gly Leu
        675                 680
```

<210> 239
<211> 680
<212> PRT
<213> Homo sapiens

<400> 239

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Ser Ser Ser Arg Gly Pro Tyr
            20                  25                  30

His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg
        35                  40                  45

Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro
    50                  55                  60

Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro
65                  70                  75                  80

Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp
                85                  90                  95

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
            100                 105                 110

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
        115                 120                 125

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
    130                 135                 140

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
145                 150                 155                 160

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
                165                 170                 175

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
            180                 185                 190

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
        195                 200                 205

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
    210                 215                 220

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
225                 230                 235                 240

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
                245                 250                 255
```

```
Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
            260                 265                 270

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
        275                 280                 285

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
    290                 295                 300

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
305                 310                 315                 320

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
                325                 330                 335

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
            340                 345                 350

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
        355                 360                 365

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
    370                 375                 380

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
385                 390                 395                 400

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
                405                 410                 415

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
            420                 425                 430

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
        435                 440                 445

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
    450                 455                 460

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
465                 470                 475                 480

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
                485                 490                 495

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
            500                 505                 510
```

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
515 520 525

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
530 535 540

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
545 550 555 560

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
565 570 575

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
580 585 590

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
595 600 605

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
610 615 620

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
625 630 635 640

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
645 650 655

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
660 665 670

Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 240
<211> 679
<212> PRT
<213> Homo sapiens

<400> 240

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Ser Ser Arg Gly Pro Tyr His
20 25 30

Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln
35 40 45

```
Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly
    50                  55                  60

Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser
65                  70                  75                  80

Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala
                85                  90                  95

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
            100                 105                 110

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
        115                 120                 125

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
    130                 135                 140

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
145                 150                 155                 160

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
                165                 170                 175

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
            180                 185                 190

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
        195                 200                 205

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn
    210                 215                 220

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
225                 230                 235                 240

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
                245                 250                 255

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
            260                 265                 270

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
        275                 280                 285

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
```

```
    290                 295                 300

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
305                 310                 315                 320

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
                325                 330                 335

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
            340                 345                 350

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
        355                 360                 365

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
    370                 375                 380

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
385                 390                 395                 400

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
                405                 410                 415

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
            420                 425                 430

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
        435                 440                 445

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
    450                 455                 460

Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
465                 470                 475                 480

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
                485                 490                 495

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
            500                 505                 510

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
        515                 520                 525

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
    530                 535                 540
```

```
Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
545                 550                 555                 560

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
                565                 570                 575

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
            580                 585                 590

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
        595                 600                 605

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
    610                 615                 620

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
625                 630                 635                 640

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
                645                 650                 655

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
            660                 665                 670

Ser Gln Ala Ala Leu Gly Leu
        675


<210>  241
<211>  678
<212>  PRT
<213>  Homo sapiens

<400>  241

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80
```

```
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His
                85                  90                  95

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
            100                 105                 110

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
        115                 120                 125

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
    130                 135                 140

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
145                 150                 155                 160

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
                165                 170                 175

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
            180                 185                 190

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
        195                 200                 205

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
    210                 215                 220

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
225                 230                 235                 240

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
                245                 250                 255

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
            260                 265                 270

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
        275                 280                 285

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
    290                 295                 300

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
305                 310                 315                 320

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
                325                 330                 335
```

```
Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
            340                 345                 350

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
        355                 360                 365

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
    370                 375                 380

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
385                 390                 395                 400

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
                405                 410                 415

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
            420                 425                 430

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
        435                 440                 445

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
    450                 455                 460

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
465                 470                 475                 480

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
                485                 490                 495

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
            500                 505                 510

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
        515                 520                 525

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
    530                 535                 540

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
545                 550                 555                 560

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
                565                 570                 575

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
            580                 585                 590
```

```
Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
        595                 600                 605

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
    610                 615                 620

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
625                 630                 635                 640

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
                645                 650                 655

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
            660                 665                 670

Gln Ala Ala Leu Gly Leu
        675
```

<210> 242
<211> 677
<212> PRT
<213> Homo sapiens

<400> 242

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Arg Gly Pro Tyr His Pro Ser
            20                  25                  30

Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile
        35                  40                  45

Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val
    50                  55                  60

Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys
65                  70                  75                  80

Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys
                85                  90                  95

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
            100                 105                 110

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
        115                 120                 125
```

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
130 135 140

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
145 150 155 160

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
165 170 175

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
180 185 190

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
195 200 205

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
210 215 220

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
225 230 235 240

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
245 250 255

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
260 265 270

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
275 280 285

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
290 295 300

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
305 310 315 320

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
325 330 335

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
340 345 350

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
355 360 365

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu

```
    370                 375                 380

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
385                 390                 395                 400

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
                405                 410                 415

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
            420                 425                 430

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
        435                 440                 445

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
    450                 455                 460

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
465                 470                 475                 480

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
                485                 490                 495

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
            500                 505                 510

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
        515                 520                 525

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
    530                 535                 540

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
545                 550                 555                 560

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
                565                 570                 575

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
            580                 585                 590

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
        595                 600                 605

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
    610                 615                 620
```

```
Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
625                 630                 635                 640

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
                645                 650                 655

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
            660                 665                 670

Ala Ala Leu Gly Leu
        675
```

<210> 243
<211> 676
<212> PRT
<213> Homo sapiens

<400> 243

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Arg Gly Pro Tyr His Pro Ser Glu
            20                  25                  30

Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met
        35                  40                  45

Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe
    50                  55                  60

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

Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser
                85                  90                  95

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
            100                 105                 110

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
        115                 120                 125

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
    130                 135                 140

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
145                 150                 155                 160
```

```
Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
                165                 170                 175

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
            180                 185                 190

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
        195                 200                 205

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
    210                 215                 220

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
225                 230                 235                 240

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
                245                 250                 255

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
            260                 265                 270

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
        275                 280                 285

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
    290                 295                 300

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
305                 310                 315                 320

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
                325                 330                 335

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
            340                 345                 350

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
        355                 360                 365

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
    370                 375                 380

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
385                 390                 395                 400

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
                405                 410                 415
```

```
Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
            420                 425                 430

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
        435                 440                 445

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
    450                 455                 460

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
465                 470                 475                 480

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
                485                 490                 495

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
            500                 505                 510

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
        515                 520                 525

Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
    530                 535                 540

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
545                 550                 555                 560

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
                565                 570                 575

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
            580                 585                 590

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
        595                 600                 605

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
    610                 615                 620

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
625                 630                 635                 640

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
                645                 650                 655

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
            660                 665                 670
```

Ala Leu Gly Leu
675

<210> 244
<211> 674
<212> PRT
<213> Homo sapiens

<400> 244

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Pro Tyr His Pro Ser Glu Cys Cys
20 25 30

Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr
35 40 45

Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr
50 55 60

Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln
65 70 75 80

Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val
85 90 95

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
100 105 110

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
115 120 125

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
130 135 140

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
145 150 155 160

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
165 170 175

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
180 185 190

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
195 200 205

```
Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
    210                 215                 220

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
225                 230                 235                 240

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
                245                 250                 255

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
            260                 265                 270

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
        275                 280                 285

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
    290                 295                 300

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
305                 310                 315                 320

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
                325                 330                 335

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
            340                 345                 350

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
        355                 360                 365

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
    370                 375                 380

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
385                 390                 395                 400

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
                405                 410                 415

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
            420                 425                 430

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
        435                 440                 445

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
```

```
    450                 455                 460

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
465                 470                 475                 480

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
                485                 490                 495

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
            500                 505                 510

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
        515                 520                 525

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
    530                 535                 540

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
545                 550                 555                 560

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
                565                 570                 575

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
            580                 585                 590

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
        595                 600                 605

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
    610                 615                 620

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
625                 630                 635                 640

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
                645                 650                 655

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
            660                 665                 670

Gly Leu


<210>  245
<211>  673
<212>  PRT
<213>  Homo sapiens
```

<400> 245

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Tyr His Pro Ser Glu Cys Cys Phe
20 25 30

Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr
35 40 45

Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys
50 55 60

Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp
65 70 75 80

Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala
85 90 95

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
100 105 110

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
115 120 125

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
130 135 140

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
145 150 155 160

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
165 170 175

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
180 185 190

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
195 200 205

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
210 215 220

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
225 230 235 240

```
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
                245                 250                 255

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
            260                 265                 270

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
        275                 280                 285

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
    290                 295                 300

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
305                 310                 315                 320

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
                325                 330                 335

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
            340                 345                 350

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
        355                 360                 365

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
    370                 375                 380

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
385                 390                 395                 400

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
                405                 410                 415

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
            420                 425                 430

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
        435                 440                 445

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
    450                 455                 460

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
465                 470                 475                 480

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
                485                 490                 495
```

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
500 505 510

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
515 520 525

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
530 535 540

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
545 550 555 560

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
565 570 575

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
580 585 590

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
595 600 605

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
610 615 620

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
625 630 635 640

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
645 650 655

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
660 665 670

Leu

<210> 246
<211> 672
<212> PRT
<213> Homo sapiens

<400> 246

Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr
20 25 30

```
Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
        35                  40                  45

Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg
    50                  55                  60

Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr
65                  70                  75                  80

Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His
                85                  90                  95

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
            100                 105                 110

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
        115                 120                 125

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
    130                 135                 140

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
145                 150                 155                 160

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
                165                 170                 175

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
            180                 185                 190

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
        195                 200                 205

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
    210                 215                 220

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
225                 230                 235                 240

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
                245                 250                 255

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
            260                 265                 270

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
        275                 280                 285
```

```
Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
    290                 295                 300

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
305                 310                 315                 320

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
                325                 330                 335

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
            340                 345                 350

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
        355                 360                 365

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
    370                 375                 380

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
385                 390                 395                 400

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
                405                 410                 415

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
            420                 425                 430

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
        435                 440                 445

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
    450                 455                 460

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
465                 470                 475                 480

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
                485                 490                 495

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
            500                 505                 510

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
        515                 520                 525

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
```

530 535 540

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
545 550 555 560

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
565 570 575

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
580 585 590

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
595 600 605

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
610 615 620

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
625 630 635 640

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
645 650 655

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 247
<211> 736
<212> PRT
<213> Homo sapiens

<400> 247

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
20 25 30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
35 40 45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
50 55 60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65 70 75 80

Asp Met Lys Glu Asn Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr

```
                85                  90                  95

Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
            100                 105                 110

Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg
        115                 120                 125

Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr
    130                 135                 140

Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His
145                 150                 155                 160

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

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
            180                 185                 190

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
        195                 200                 205

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
    210                 215                 220

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
225                 230                 235                 240

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
                245                 250                 255

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
            260                 265                 270

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
        275                 280                 285

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
    290                 295                 300

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
305                 310                 315                 320

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
                325                 330                 335
```

```
Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
            340                 345                 350

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
        355                 360                 365

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
    370                 375                 380

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
385                 390                 395                 400

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
                405                 410                 415

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
            420                 425                 430

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
        435                 440                 445

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
    450                 455                 460

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
465                 470                 475                 480

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
                485                 490                 495

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
            500                 505                 510

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
        515                 520                 525

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
    530                 535                 540

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
545                 550                 555                 560

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
                565                 570                 575

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
            580                 585                 590
```

```
Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
        595                 600                 605

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
    610                 615                 620

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
625                 630                 635                 640

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
                645                 650                 655

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
            660                 665                 670

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
        675                 680                 685

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
    690                 695                 700

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
705                 710                 715                 720

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                725                 730                 735


<210>  248
<211>  700
<212>  PRT
<213>  Homo sapiens

<400>  248

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
            20                  25                  30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
        35                  40                  45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
    50                  55                  60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65                  70                  75                  80
```

```
Asp Met Lys Glu Asn His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser
                85                  90                  95

Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val
            100                 105                 110

Lys Gly Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
        115                 120                 125

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
    130                 135                 140

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
145                 150                 155                 160

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
                165                 170                 175

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
            180                 185                 190

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
        195                 200                 205

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
    210                 215                 220

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
225                 230                 235                 240

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
                245                 250                 255

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
            260                 265                 270

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
        275                 280                 285

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
    290                 295                 300

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
305                 310                 315                 320

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
                325                 330                 335
```

```
Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
            340                 345                 350

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
        355                 360                 365

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
    370                 375                 380

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
385                 390                 395                 400

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
                405                 410                 415

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
            420                 425                 430

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
        435                 440                 445

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
    450                 455                 460

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
465                 470                 475                 480

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
                485                 490                 495

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
            500                 505                 510

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
        515                 520                 525

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
    530                 535                 540

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
545                 550                 555                 560

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
                565                 570                 575

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
```

580 585 590

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
595 600 605

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
610 615 620

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
625 630 635 640

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
645 650 655

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
660 665 670

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
675 680 685

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
690 695 700

<210> 249
<211> 686
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (580)..(580)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 249

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
20 25 30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
35 40 45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
50 55 60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65 70 75 80

```
Asp Met Lys Glu Asn Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
                85                  90                  95

Gly Gly Gly Gly Ser Asp Ala His Lys Ser Glu Val Ala His Arg Phe
            100                 105                 110

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
        115                 120                 125

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
    130                 135                 140

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
145                 150                 155                 160

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
                165                 170                 175

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
            180                 185                 190

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
        195                 200                 205

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
    210                 215                 220

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
225                 230                 235                 240

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
                245                 250                 255

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
            260                 265                 270

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
        275                 280                 285

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
    290                 295                 300

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
305                 310                 315                 320

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
                325                 330                 335
```

```
Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
            340                 345                 350

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
        355                 360                 365

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
    370                 375                 380

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
385                 390                 395                 400

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
                405                 410                 415

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
            420                 425                 430

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
        435                 440                 445

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
    450                 455                 460

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
465                 470                 475                 480

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
                485                 490                 495

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
            500                 505                 510

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
        515                 520                 525

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
    530                 535                 540

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
545                 550                 555                 560

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
                565                 570                 575

Cys Cys Thr Xaa Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
```

580 585 590

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
595 600 605

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
610 615 620

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
625 630 635 640

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
645 650 655

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
660 665 670

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
675 680 685

<210> 250
<211> 669
<212> PRT
<213> Homo sapiens

<400> 250

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr
20 25 30

Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser
35 40 45

Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser
50 55 60

Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp
65 70 75 80

Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
85 90 95

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
100 105 110

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn

```
        115                 120                 125

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
    130                 135                 140

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
145                 150                 155                 160

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
                165                 170                 175

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
            180                 185                 190

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
        195                 200                 205

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
    210                 215                 220

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
225                 230                 235                 240

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
                245                 250                 255

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
            260                 265                 270

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
        275                 280                 285

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
    290                 295                 300

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
305                 310                 315                 320

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
                325                 330                 335

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
            340                 345                 350

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
        355                 360                 365
```

```
Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
    370                 375                 380

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
385                 390                 395                 400

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
                405                 410                 415

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
            420                 425                 430

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
        435                 440                 445

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
    450                 455                 460

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
465                 470                 475                 480

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
                485                 490                 495

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
            500                 505                 510

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
        515                 520                 525

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
    530                 535                 540

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
545                 550                 555                 560

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
                565                 570                 575

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
            580                 585                 590

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
        595                 600                 605

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
    610                 615                 620
```

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Cys Val Glu
625 630 635 640

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
645 650 655

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665

<210> 251
<211> 671
<212> PRT
<213> Homo sapiens

<400> 251

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr
20 25 30

Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr
35 40 45

Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly
50 55 60

His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile
65 70 75 80

Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg
85 90 95

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
100 105 110

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
115 120 125

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
130 135 140

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
145 150 155 160

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
165 170 175

```
Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
            180                 185                 190

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
        195                 200                 205

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
    210                 215                 220

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
225                 230                 235                 240

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
                245                 250                 255

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
            260                 265                 270

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
        275                 280                 285

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
    290                 295                 300

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
305                 310                 315                 320

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
                325                 330                 335

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
            340                 345                 350

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
        355                 360                 365

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
    370                 375                 380

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
385                 390                 395                 400

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
                405                 410                 415

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
            420                 425                 430
```

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
435 440 445

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
450 455 460

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
465 470 475 480

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
485 490 495

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
500 505 510

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
515 520 525

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
530 535 540

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
545 550 555 560

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
565 570 575

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
580 585 590

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
595 600 605

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
610 615 620

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
625 630 635 640

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
645 650 655

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 252

<211> 686
<212> PRT
<213> Homo sapiens

<400> 252

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
20 25 30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
35 40 45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
50 55 60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65 70 75 80

Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe
85 90 95

Lys Asp Leu Gly Glu Asp Ala His Lys Ser Glu Val Ala His Arg Phe
100 105 110

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
115 120 125

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
130 135 140

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
145 150 155 160

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
165 170 175

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
180 185 190

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
195 200 205

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
210 215 220

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu

```
225                 230                 235                 240

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
                245                 250                 255

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
            260                 265                 270

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
        275                 280                 285

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
    290                 295                 300

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
305                 310                 315                 320

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
                325                 330                 335

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
            340                 345                 350

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
        355                 360                 365

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
    370                 375                 380

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
385                 390                 395                 400

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
                405                 410                 415

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
            420                 425                 430

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
        435                 440                 445

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
    450                 455                 460

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
465                 470                 475                 480
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```
Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
                485                 490                 495

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
            500                 505                 510

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
        515                 520                 525

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
    530                 535                 540

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
545                 550                 555                 560

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
                565                 570                 575

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
            580                 585                 590

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
        595                 600                 605

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
    610                 615                 620

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
625                 630                 635                 640

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
                645                 650                 655

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
            660                 665                 670

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        675                 680                 685


<210>  253
<211>  672
<212>  PRT
<213>  Homo sapiens

<400>  253

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15
```

```
Ile Ser Ala Met Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr
            20                  25                  30

Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
        35                  40                  45

Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg
    50                  55                  60

Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr
65                  70                  75                  80

Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His
                85                  90                  95

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
            100                 105                 110

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
        115                 120                 125

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
    130                 135                 140

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
145                 150                 155                 160

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
                165                 170                 175

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
            180                 185                 190

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
        195                 200                 205

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
    210                 215                 220

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
225                 230                 235                 240

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
                245                 250                 255

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
            260                 265                 270
```

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
275 280 285

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
290 295 300

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
305 310 315 320

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
325 330 335

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
340 345 350

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
355 360 365

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
370 375 380

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
385 390 395 400

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
405 410 415

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
420 425 430

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
435 440 445

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
450 455 460

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
465 470 475 480

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
485 490 495

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
500 505 510

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
515 520 525

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
530 535 540

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
545 550 555 560

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
565 570 575

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
580 585 590

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
595 600 605

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
610 615 620

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
625 630 635 640

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
645 650 655

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 254
<211> 673
<212> PRT
<213> Homo sapiens

<400> 254

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Met Ser Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe
20 25 30

Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr
35 40 45

Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys
50 55 60

Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp
65 70 75 80

```
Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala
                85                  90                  95

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
            100                 105                 110

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
        115                 120                 125

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
    130                 135                 140

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
145                 150                 155                 160

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
                165                 170                 175

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
            180                 185                 190

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
        195                 200                 205

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
    210                 215                 220

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
225                 230                 235                 240

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
                245                 250                 255

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
            260                 265                 270

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
        275                 280                 285

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
    290                 295                 300

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
305                 310                 315                 320

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
```

325 330 335

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
340 345 350

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
355 360 365

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
370 375 380

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
385 390 395 400

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
405 410 415

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
420 425 430

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
435 440 445

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
450 455 460

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
465 470 475 480

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
485 490 495

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
500 505 510

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
515 520 525

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
530 535 540

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
545 550 555 560

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
565 570 575

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
580 585 590

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
595 600 605

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
610 615 620

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
625 630 635 640

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
645 650 655

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
660 665 670

Leu

<210> 255
<211> 673
<212> PRT
<213> Homo sapiens

<400> 255

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Met Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys Cys
20 25 30

Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr
35 40 45

Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr
50 55 60

Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln
65 70 75 80

Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val
85 90 95

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
100 105 110

```
Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
        115                 120                 125

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
    130                 135                 140

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
145                 150                 155                 160

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
                165                 170                 175

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
            180                 185                 190

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
        195                 200                 205

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
    210                 215                 220

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
225                 230                 235                 240

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
                245                 250                 255

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
            260                 265                 270

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
        275                 280                 285

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
    290                 295                 300

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
305                 310                 315                 320

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
                325                 330                 335

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
            340                 345                 350

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
        355                 360                 365
```

```
Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
    370                 375                 380

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
385                 390                 395                 400

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
                405                 410                 415

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
            420                 425                 430

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
        435                 440                 445

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
    450                 455                 460

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
465                 470                 475                 480

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
                485                 490                 495

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
            500                 505                 510

Val Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
        515                 520                 525

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
    530                 535                 540

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
545                 550                 555                 560

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
                565                 570                 575

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
            580                 585                 590

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
        595                 600                 605

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
    610                 615                 620
```

```
Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
625                 630                 635                 640

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
                645                 650                 655

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
            660                 665                 670

Leu
```

<210> 256
<211> 671
<212> PRT
<213> Homo sapiens

<400> 256

```
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala Met Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr
            20                  25                  30

Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr
        35                  40                  45

Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly
    50                  55                  60

His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile
65                  70                  75                  80

Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg
                85                  90                  95

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
            100                 105                 110

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
        115                 120                 125

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
    130                 135                 140

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
145                 150                 155                 160
```

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
165 170 175

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
180 185 190

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
195 200 205

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
210 215 220

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
225 230 235 240

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
245 250 255

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
260 265 270

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
275 280 285

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
290 295 300

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
305 310 315 320

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
325 330 335

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
340 345 350

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
355 360 365

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
370 375 380

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
385 390 395 400

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe

405 410 415

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
420 425 430

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
435 440 445

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
450 455 460

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
465 470 475 480

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
485 490 495

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
500 505 510

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
515 520 525

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
530 535 540

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
545 550 555 560

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
565 570 575

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
580 585 590

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
595 600 605

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
610 615 620

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
625 630 635 640

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
645 650 655

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 257
<211> 670
<212> PRT
<213> Homo sapiens

<400> 257

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Met Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
20 25 30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
35 40 45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
50 55 60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65 70 75 80

Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe
85 90 95

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
100 105 110

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
115 120 125

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
130 135 140

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
145 150 155 160

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
165 170 175

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
180 185 190

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
195 200 205

```
Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
    210                 215                 220

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
225                 230                 235                 240

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
                245                 250                 255

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
            260                 265                 270

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
        275                 280                 285

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
    290                 295                 300

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
305                 310                 315                 320

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
                325                 330                 335

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
            340                 345                 350

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
        355                 360                 365

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
    370                 375                 380

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
385                 390                 395                 400

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
                405                 410                 415

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
            420                 425                 430

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
        435                 440                 445

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
    450                 455                 460
```

```
Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
465                 470                 475                 480

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
                485                 490                 495

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
            500                 505                 510

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
        515                 520                 525

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
    530                 535                 540

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
545                 550                 555                 560

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
                565                 570                 575

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
            580                 585                 590

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
        595                 600                 605

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
    610                 615                 620

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
625                 630                 635                 640

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
                645                 650                 655

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
            660                 665                 670

<210>  258
<211>  680
<212>  PRT
<213>  Homo sapiens

<400>  258

Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1               5                   10                  15
```

```
Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Gly Pro Tyr
            20                  25                  30

His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg
        35                  40                  45

Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro
    50                  55                  60

Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro
65                  70                  75                  80

Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp
                85                  90                  95

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
            100                 105                 110

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
        115                 120                 125

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
    130                 135                 140

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
145                 150                 155                 160

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
                165                 170                 175

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
            180                 185                 190

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
        195                 200                 205

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
    210                 215                 220

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
225                 230                 235                 240

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
                245                 250                 255

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
            260                 265                 270
```

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
275 280 285

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
290 295 300

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
305 310 315 320

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
325 330 335

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
340 345 350

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
355 360 365

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
370 375 380

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
385 390 395 400

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
405 410 415

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
420 425 430

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
435 440 445

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
450 455 460

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
465 470 475 480

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
485 490 495

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
500 505 510

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val

515 520 525

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
530 535 540

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
545 550 555 560

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
565 570 575

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
580 585 590

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
595 600 605

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
610 615 620

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
625 630 635 640

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
645 650 655

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
660 665 670

Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 259
<211> 682
<212> PRT
<213> Homo sapiens

<400> 259

Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg His Ala Gly
20 25 30

Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile
35 40 45

Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser

```
    50                  55                  60

Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr
65                  70                  75                  80

Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu
                85                  90                  95

Asn Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
            100                 105                 110

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
        115                 120                 125

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
    130                 135                 140

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
145                 150                 155                 160

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
                165                 170                 175

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
            180                 185                 190

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
        195                 200                 205

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
    210                 215                 220

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
225                 230                 235                 240

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
                245                 250                 255

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
            260                 265                 270

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
        275                 280                 285

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
    290                 295                 300
```

```
Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
305                 310                 315                 320

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
                325                 330                 335

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
            340                 345                 350

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
        355                 360                 365

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
    370                 375                 380

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
385                 390                 395                 400

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
                405                 410                 415

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
            420                 425                 430

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
        435                 440                 445

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
    450                 455                 460

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
465                 470                 475                 480

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
                485                 490                 495

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
            500                 505                 510

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
        515                 520                 525

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
    530                 535                 540

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
545                 550                 555                 560
```

```
His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
                565                 570                 575

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
            580                 585                 590

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
        595                 600                 605

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
    610                 615                 620

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
625                 630                 635                 640

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
                645                 650                 655

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
            660                 665                 670

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        675                 680
```

<210> 260
<211> 678
<212> PRT
<213> Homo sapiens

<400> 260

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Pro Ile Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His
                85                  90                  95
```

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
100 105 110

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
115 120 125

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
130 135 140

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
145 150 155 160

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
165 170 175

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
180 185 190

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
195 200 205

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
210 215 220

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
225 230 235 240

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
245 250 255

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
260 265 270

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
275 280 285

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
290 295 300

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
305 310 315 320

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
325 330 335

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
340 345 350

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
355 360 365

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
370 375 380

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
385 390 395 400

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
405 410 415

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
420 425 430

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
435 440 445

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
450 455 460

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
465 470 475 480

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
485 490 495

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
500 505 510

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
515 520 525

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
530 535 540

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
545 550 555 560

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
565 570 575

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
580 585 590

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr

595 600 605

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
610 615 620

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
625 630 635 640

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
645 650 655

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
660 665 670

Gln Ala Ala Leu Gly Leu
675

<210> 261
<211> 678
<212> PRT
<213> Homo sapiens

<400> 261

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala Ser Leu Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His
85 90 95

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
100 105 110

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
115 120 125

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys

```
    130                 135                 140

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
145                 150                 155                 160

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
                165                 170                 175

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
            180                 185                 190

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
        195                 200                 205

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
    210                 215                 220

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
225                 230                 235                 240

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
                245                 250                 255

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
            260                 265                 270

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
        275                 280                 285

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
    290                 295                 300

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
305                 310                 315                 320

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
                325                 330                 335

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
            340                 345                 350

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
        355                 360                 365

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
    370                 375                 380
```

```
Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
385                 390                 395                 400

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
                405                 410                 415

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
            420                 425                 430

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
        435                 440                 445

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
    450                 455                 460

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
465                 470                 475                 480

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
                485                 490                 495

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
            500                 505                 510

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
        515                 520                 525

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
    530                 535                 540

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
545                 550                 555                 560

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
                565                 570                 575

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
            580                 585                 590

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
        595                 600                 605

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
    610                 615                 620

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
625                 630                 635                 640
```

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
645 650 655

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
660 665 670

Gln Ala Ala Leu Gly Leu
675

<210> 262
<211> 678
<212> PRT
<213> Homo sapiens

<400> 262

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Tyr Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His
85 90 95

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
100 105 110

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
115 120 125

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
130 135 140

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
145 150 155 160

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
165 170 175

```
Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
            180                 185                 190

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
        195                 200                 205

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
    210                 215                 220

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
225                 230                 235                 240

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
                245                 250                 255

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
            260                 265                 270

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
        275                 280                 285

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
    290                 295                 300

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
305                 310                 315                 320

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
                325                 330                 335

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
            340                 345                 350

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
        355                 360                 365

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
    370                 375                 380

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
385                 390                 395                 400

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
                405                 410                 415

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
            420                 425                 430
```

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
435 440 445

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
450 455 460

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
465 470 475 480

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
485 490 495

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
500 505 510

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
515 520 525

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
530 535 540

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
545 550 555 560

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
565 570 575

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
580 585 590

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
595 600 605

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
610 615 620

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
625 630 635 640

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
645 650 655

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
660 665 670

Gln Ala Ala Leu Gly Leu

675

<210> 263
<211> 679
<212> PRT
<213> Homo sapiens

<400> 263

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Met Ser Pro Tyr Gly Pro Tyr His
20 25 30

Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln
35 40 45

Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly
50 55 60

Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser
65 70 75 80

Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala
85 90 95

His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn
100 105 110

Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys
115 120 125

Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala
130 135 140

Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu
145 150 155 160

His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu
165 170 175

Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg
180 185 190

Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg
195 200 205

Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn

```
    210                 215                 220

Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His
225                 230                 235                 240

Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys
                245                 250                 255

Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu
            260                 265                 270

Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala
        275                 280                 285

Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala
    290                 295                 300

Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala
305                 310                 315                 320

Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His
                325                 330                 335

Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
            340                 345                 350

Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys
        355                 360                 365

Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile
    370                 375                 380

Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala
385                 390                 395                 400

Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala
                405                 410                 415

Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His
            420                 425                 430

Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu
        435                 440                 445

Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr
    450                 455                 460
```

```
Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn
465                 470                 475                 480

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
                485                 490                 495

Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
            500                 505                 510

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
        515                 520                 525

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
    530                 535                 540

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
545                 550                 555                 560

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
                565                 570                 575

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
            580                 585                 590

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
        595                 600                 605

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
    610                 615                 620

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
625                 630                 635                 640

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
                645                 650                 655

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
            660                 665                 670

Ser Gln Ala Ala Leu Gly Leu
        675
```

<210> 264
<211> 680
<212> PRT
<213> Homo sapiens

<400> 264

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Cys Pro Tyr Ser Cys Gly Pro Tyr
            20                  25                  30

His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg
        35                  40                  45

Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro
    50                  55                  60

Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro
65                  70                  75                  80

Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp
                85                  90                  95

Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu
            100                 105                 110

Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln
        115                 120                 125

Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe
    130                 135                 140

Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser
145                 150                 155                 160

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg
                165                 170                 175

Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu
            180                 185                 190

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro
        195                 200                 205

Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp
    210                 215                 220

Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg
225                 230                 235                 240

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr
                245                 250                 255
```

Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys
260 265 270

Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser
275 280 285

Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg
290 295 300

Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys
305 310 315 320

Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val
325 330 335

His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
340 345 350

Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser
355 360 365

Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys
370 375 380

Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu
385 390 395 400

Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu
405 410 415

Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg
420 425 430

His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr
435 440 445

Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys
450 455 460

Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln
465 470 475 480

Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr
485 490 495

Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln
500 505 510

Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val
515 520 525

Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala
530 535 540

Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu
545 550 555 560

Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu
565 570 575

Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr
580 585 590

Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile
595 600 605

Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu
610 615 620

Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys
625 630 635 640

Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala
645 650 655

Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala
660 665 670

Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 265
<211> 678
<212> PRT
<213> Homo sapiens

<400> 265

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Pro Tyr Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His
85 90 95

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
100 105 110

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
115 120 125

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
130 135 140

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
145 150 155 160

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
165 170 175

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
180 185 190

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
195 200 205

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
210 215 220

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
225 230 235 240

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
245 250 255

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
260 265 270

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
275 280 285

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe

```
    290                 295                 300

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
305                 310                 315                 320

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
                325                 330                 335

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
            340                 345                 350

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
        355                 360                 365

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
    370                 375                 380

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
385                 390                 395                 400

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
                405                 410                 415

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
            420                 425                 430

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
        435                 440                 445

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
    450                 455                 460

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
465                 470                 475                 480

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
                485                 490                 495

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
            500                 505                 510

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
        515                 520                 525

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
    530                 535                 540
```

```
Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
545                 550                 555                 560

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
                565                 570                 575

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
            580                 585                 590

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
        595                 600                 605

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
    610                 615                 620

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
625                 630                 635                 640

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
                645                 650                 655

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
            660                 665                 670

Gln Ala Ala Leu Gly Leu
        675


<210>  266
<211>  736
<212>  PRT
<213>  Homo sapiens

<400>  266

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr
            20                  25                  30

Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn
        35                  40                  45

Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His
    50                  55                  60

Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys
65                  70                  75                  80
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```
Asp Met Lys Glu Asn Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr
                85                  90                  95

Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu
            100                 105                 110

Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg
        115                 120                 125

Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr
    130                 135                 140

Ile Lys Asp Met Lys Glu Asn Asp Ala His Lys Ser Glu Val Ala His
145                 150                 155                 160

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

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
            180                 185                 190

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
        195                 200                 205

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
    210                 215                 220

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
225                 230                 235                 240

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
                245                 250                 255

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
            260                 265                 270

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
        275                 280                 285

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
    290                 295                 300

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
305                 310                 315                 320

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
                325                 330                 335
```

```
Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
            340                 345                 350

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
        355                 360                 365

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
    370                 375                 380

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
385                 390                 395                 400

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
                405                 410                 415

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
            420                 425                 430

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
        435                 440                 445

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
    450                 455                 460

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
465                 470                 475                 480

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
                485                 490                 495

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
            500                 505                 510

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
        515                 520                 525

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
    530                 535                 540

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
545                 550                 555                 560

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
                565                 570                 575

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
            580                 585                 590
```

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
595 600 605

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
610 615 620

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
625 630 635 640

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
645 650 655

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
660 665 670

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
675 680 685

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
690 695 700

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
705 710 715 720

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
725 730 735

<210> 267
<211> 165
<212> PRT
<213> Homo sapiens

<400> 267

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 268
<211> 165
<212> PRT
<213> Homo sapiens

<400> 268

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 269
<211> 165
<212> PRT
<213> Homo sapiens

<400> 269

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 270
<211> 165
<212> PRT
<213> Homo sapiens

<400> 270

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 271
<211> 165
<212> PRT
<213> Homo sapiens

<400> 271

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

```
Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210>  272
<211>  165
<212>  PRT
<213>  Homo sapiens

<400>  272

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
```

```
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165
```

<210> 273
<211> 165
<212> PRT
<213> Homo sapiens

<400> 273

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110
```

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 274
<211> 165
<212> PRT
<213> Homo sapiens

<400> 274

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 275
<211> 165
<212> PRT
<213> Homo sapiens

<400> 275

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 276
<211> 165
<212> PRT
<213> Homo sapiens

<400> 276

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165
```

<210> 277
<211> 165
<212> PRT
<213> Homo sapiens

<400> 277

```
Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45
```

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 278
<211> 32
<212> PRT
<213> Homo sapiens

<400> 278

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 279
<211> 32
<212> PRT
<213> Homo sapiens

<400> 279

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 280

<211> 29
<212> PRT
<213> Homo sapiens

<400> 280

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
20 25

<210> 281
<211> 32
<212> PRT
<213> Homo sapiens

<400> 281

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 282
<211> 32
<212> PRT
<213> Homo sapiens

<400> 282

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 283
<211> 32
<212> PRT
<213> Homo sapiens

<400> 283

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 284
<211> 32
<212> PRT
<213> Homo sapiens

<400> 284

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 285
<211> 32
<212> PRT
<213> Homo sapiens

<400> 285

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Gly Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 286
<211> 29
<212> PRT
<213> Homo sapiens

<400> 286

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
20 25

<210> 287
<211> 32
<212> PRT
<213> Homo sapiens

<400> 287

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Gly Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 288
<211> 32
<212> PRT
<213> Homo sapiens

<400> 288

```
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Gly Met Asp
1               5                   10                  15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
            20                  25                  30
```

<210> 289
<211> 32
<212> PRT
<213> Homo sapiens

<400> 289

```
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1               5                   10                  15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
            20                  25                  30
```

<210> 290
<211> 30
<212> PRT
<213> Homo sapiens

<400> 290

```
Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1               5                   10                  15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg
            20                  25                  30
```

<210> 291
<211> 151
<212> PRT
<213> Homo sapiens

<400> 291

```
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1               5                   10                  15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20                  25                  30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35                  40                  45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50                  55                  60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65                  70                  75                  80
```

```
Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140

Gly Cys Asn Ser Phe Arg Tyr
145                 150
```

<210> 292
<211> 151
<212> PRT
<213> Homo sapiens

<400> 292

```
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1               5                   10                  15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20                  25                  30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35                  40                  45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50                  55                  60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65                  70                  75                  80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140
```

Gly Cys Asn Ser Phe Arg Tyr
145 150

<210> 293
<211> 151
<212> PRT
<213> Homo sapiens

<400> 293

Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1 5 10 15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
20 25 30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
35 40 45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
50 55 60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65 70 75 80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
85 90 95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
100 105 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
115 120 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
130 135 140

Gly Cys Asn Ser Phe Arg Tyr
145 150

<210> 294
<211> 151
<212> PRT
<213> Homo sapiens

<400> 294

Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1 5 10 15

```
Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20                  25                  30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35                  40                  45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50                  55                  60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65                  70                  75                  80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140

Gly Cys Asn Ser Phe Arg Tyr
145                 150


<210>  295
<211>  151
<212>  PRT
<213>  Homo sapiens

<400>  295

Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1               5                   10                  15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20                  25                  30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35                  40                  45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50                  55                  60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65                  70                  75                  80
```

```
Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140

Gly Cys Asn Ser Phe Arg Tyr
145                 150
```

<210> 296
<211> 151
<212> PRT
<213> Homo sapiens

<400> 296

```
Met Ser Ser Phe Ser Thr Thr Thr Val Ser Phe Leu Leu Leu Leu Ala
1               5                   10                  15

Phe Gln Leu Leu Gly Gln Thr Arg Ala Asn Pro Met Tyr Asn Ala Val
            20                  25                  30

Ser Asn Ala Asp Leu Met Asp Phe Lys Asn Leu Leu Asp His Leu Glu
        35                  40                  45

Glu Lys Met Pro Leu Glu Asp Glu Val Val Pro Pro Gln Val Leu Ser
    50                  55                  60

Glu Pro Asn Glu Glu Ala Gly Ala Ala Leu Ser Pro Leu Pro Glu Val
65                  70                  75                  80

Pro Pro Trp Thr Gly Glu Val Ser Pro Ala Gln Arg Asp Gly Gly Ala
                85                  90                  95

Leu Gly Arg Gly Pro Trp Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys
            100                 105                 110

Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro Arg Ser Leu Arg Arg Ser
        115                 120                 125

Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu
    130                 135                 140
```

```
Gly Cys Asn Ser Phe Arg Tyr
145                 150


<210>  297
<211>  126
<212>  PRT
<213>  Homo sapiens

<400>  297

Met His Leu Ser Gln Leu Leu Ala Cys Ala Leu Leu Leu Thr Leu Leu
1               5                   10                  15


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


Arg Thr Pro Pro Ala Glu Glu Leu Ala Glu Pro Gln Ala Ala Gly Gly
        35                  40                  45


Gly Gln Lys Lys Gly Asp Lys Ala Pro Gly Gly Gly Gly Ala Asn Leu
    50                  55                  60


Lys Gly Asp Arg Ser Arg Leu Leu Arg Asp Leu Arg Val Asp Thr Lys
65                  70                  75                  80


Ser Arg Ala Ala Trp Ala Arg Leu Leu Gln Glu His Pro Asn Ala Arg
                85                  90                  95


Lys Tyr Lys Gly Ala Asn Lys Lys Gly Leu Ser Lys Gly Cys Phe Gly
            100                 105                 110


Leu Lys Leu Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys
        115                 120                 125


<210>  298
<211>  126
<212>  PRT
<213>  Homo sapiens

<400>  298

Met His Leu Ser Gln Leu Leu Ala Cys Ala Leu Leu Leu Thr Leu Leu
1               5                   10                  15


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


Arg Thr Pro Pro Ala Glu Glu Leu Ala Glu Pro Gln Ala Ala Gly Gly
        35                  40                  45
```

Gly Gln Lys Lys Gly Asp Lys Ala Pro Gly Gly Gly Gly Ala Asn Leu
50 55 60

Lys Gly Asp Arg Ser Arg Leu Leu Arg Asp Leu Arg Val Asp Thr Lys
65 70 75 80

Ser Arg Ala Ala Trp Ala Arg Leu Leu Gln Glu His Pro Asn Ala Arg
85 90 95

Lys Tyr Lys Gly Ala Asn Lys Lys Gly Leu Ser Lys Gly Cys Phe Gly
100 105 110

Leu Lys Leu Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys
115 120 125

<210> 299
<211> 38
<212> PRT
<213> Dendroaspis angusticeps

<400> 299

Glu Val Lys Tyr Asp Pro Cys Phe Gly His Lys Ile Asp Arg Ile Asn
1 5 10 15

His Val Ser Asn Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro Asn
20 25 30

Ala Pro Ser Thr Ser Ala
35

<210> 300
<211> 38
<212> PRT
<213> Dendroaspis angusticeps

<400> 300

Glu Val Lys Tyr Asp Pro Cys Phe Gly His Lys Ile Asp Arg Ile Asn
1 5 10 15

His Val Ser Asn Leu Gly Cys Pro Ser Leu Arg Asp Pro Arg Pro Asn
20 25 30

Ala Pro Ser Thr Ser Ala
35

<210> 301
<211> 32
<212> PRT
<213> Homo sapiens

<400> 301

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 302
<211> 28
<212> PRT
<213> Homo sapiens

<400> 302

Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly
1 5 10 15

Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
20 25

<210> 303
<211> 93
<212> PRT
<213> Homo sapiens

<400> 303

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 304
<211> 93
<212> PRT
<213> Homo sapiens

<400> 304

```
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1               5                  10                  15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
```

<210> 305
<211> 93
<212> PRT
<213> Homo sapiens

<400> 305

```
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1               5                  10                  15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
```

<210> 306
<211> 93
<212> PRT
<213> Homo sapiens

<400> 306

```
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
```

1 5 10 15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 307
<211> 93
<212> PRT
<213> Homo sapiens

<400> 307

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 308
<211> 93
<212> PRT
<213> Homo sapiens

<400> 308

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 309
<211> 93
<212> PRT
<213> Homo sapiens

<400> 309

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 310
<211> 93
<212> PRT
<213> Homo sapiens

<400> 310

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 311
<211> 93
<212> PRT
<213> Homo sapiens

<400> 311

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 312
<211> 74
<212> PRT
<213> Homo sapiens

<400> 312

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 313
<211> 74
<212> PRT
<213> Homo sapiens

<400> 313

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 314
<211> 74
<212> PRT
<213> Homo sapiens

<400> 314

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val

50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 315
<211> 74
<212> PRT
<213> Homo sapiens

<400> 315

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 316
<211> 74
<212> PRT
<213> Homo sapiens

<400> 316

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 317
<211> 74

<212> PRT
<213> Homo sapiens

<400> 317

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 318
<211> 74
<212> PRT
<213> Homo sapiens

<400> 318

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 319
<211> 74
<212> PRT
<213> Homo sapiens

<400> 319

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 320
<211> 74
<212> PRT
<213> Homo sapiens

<400> 320

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 321
<211> 74
<212> PRT
<213> Homo sapiens

<400> 321

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Glu Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val

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    50                  55                  60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65                  70
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<210> 322
<211> 93
<212> PRT
<213> Homo sapiens

<400> 322

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
                85                  90
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<210> 323
<211> 93
<212> PRT
<213> Homo sapiens

<400> 323

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80
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Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 324
<211> 93
<212> PRT
<213> Homo sapiens

<400> 324

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 325
<211> 65
<212> PRT
<213> Homo sapiens

<400> 325

Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile
1 5 10 15

Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser
20 25 30

Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr
35 40 45

Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu
50 55 60

Asn
65

<210> 326
<211> 67
<212> PRT
<213> Homo sapiens

<400> 326

Arg Gly Pro Tyr His Pro Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr
1 5 10 15

Lys Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln
20 25 30

Cys Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val
35 40 45

Cys Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met
50 55 60

Lys Glu Asn
65

<210> 327
<211> 66
<212> PRT
<213> Homo sapiens

<400> 327

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 328
<211> 93
<212> PRT
<213> Homo sapiens

<400> 328

Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile

1 5 10 15

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 329
<211> 93
<212> PRT
<213> Homo sapiens

<400> 329

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 330
<211> 93
<212> PRT
<213> Homo sapiens

<400> 330

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 331
<211> 93
<212> PRT
<213> Homo sapiens

<400> 331

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 332
<211> 93
<212> PRT
<213> Homo sapiens

<400> 332

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 333
<211> 66
<212> PRT
<213> Homo sapiens

<400> 333

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 334
<211> 66
<212> PRT
<213> Homo sapiens

<400> 334

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 335
<211> 66
<212> PRT
<213> Homo sapiens

<400> 335

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 336
<211> 66
<212> PRT
<213> Homo sapiens

<400> 336

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn

65

<210> 337
<211> 66
<212> PRT
<213> Homo sapiens

<400> 337

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 338
<211> 66
<212> PRT
<213> Homo sapiens

<400> 338

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 339
<211> 66
<212> PRT
<213> Homo sapiens

<400> 339

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 340
<211> 66
<212> PRT
<213> Homo sapiens

<400> 340

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

Ile Pro Arg Gln Arg Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys
20 25 30

Ser Lys Pro Gly Ile Val Phe Ile Thr Lys Arg Gly His Ser Val Cys
35 40 45

Thr Asn Pro Ser Asp Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys
50 55 60

Glu Asn
65

<210> 341
<211> 93
<212> PRT
<213> Homo sapiens

<400> 341

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

Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30

Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 342
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<212> DNA
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<400> 342
catacaaact taagagtcca 20

<210> 343
<211> 56
<212> DNA
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<400> 343
ctttaaatcg atgagcaacc tcactcttgt gtgcatcagc gttagccaaa gaagca 56

<210> 344
<211> 20
<212> DNA
<213> Homo sapiens

<400> 344
catacaaact taagagtcca 20

<210> 345
<211> 56
<212> DNA
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<400> 345
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<210> 346
<211> 20
<212> DNA
<213> Homo sapiens

<400> 346
catacaaact taagagtcca 20

<210> 347
<211> 56

<212> DNA
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<400> 347
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<210> 348
<211> 41
<212> DNA
<213> Homo sapiens

<400> 348
cgcgcgcgtc gacaaaagat gtgatctgcc tcaaacccac a 41

<210> 349
<211> 59
<212> DNA
<213> Homo sapiens

<400> 349
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 350
<211> 27
<212> DNA
<213> Homo sapiens

<400> 350
gttagcagag tagcagggct ttcggct 27

<210> 351
<211> 59
<212> DNA
<213> Homo sapiens

<400> 351
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 352
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<212> DNA
<213> Homo sapiens

<400> 352
cgcgcgcgtc gacaaaagat gtgatctgcc tcaaacccac a 41

<210> 353
<211> 59
<212> DNA
<213> Homo sapiens

<400> 353
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 354
<211> 38

<212> DNA
<213> Homo sapiens

<400> 354
caagctgcct taggcttatg tgatctgcct caaaccca 38

<210> 355
<211> 39
<212> DNA
<213> Homo sapiens

<400> 355
gaattcggcg cgccttattc cttacttctt aaactttct 39

<210> 356
<211> 107
<212> DNA
<213> Homo sapiens

<400> 356
gcgcgcggat ccgccaccat ggccttgacc tttgctttac tggtggccct cctggtgctc 60

agctgcaagt caagctgctc tgtgggctgt gatctgcctc aaaccca 107

<210> 357
<211> 59
<212> DNA
<213> Homo sapiens

<400> 357
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 358
<211> 25
<212> DNA
<213> Homo sapiens

<400> 358
gcatgtgatc tgcctcaaac ccaca 25

<210> 359
<211> 59
<212> DNA
<213> Homo sapiens

<400> 359
gcgcgcatcg atgagcaacc tcactcttgt gtgcatcttc cttacttctt aaactttct 59

<210> 360
<211> 20
<212> DNA
<213> Homo sapiens

<400> 360
catacaaact taagagtcca 20

<210> 361
<211> 67
<212> DNA
<213> Homo sapiens

<400> 361
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aagccga 67

<210> 362
<211> 103
<212> DNA
<213> Homo sapiens

<400> 362
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ttactgccct tggatcccag gccagcccca agatggtgca agg 103

<210> 363
<211> 57
<212> DNA
<213> Homo sapiens

<400> 363
agtcccatcg atgagcaacc tcactcttgt gtgcatcatg ccgcctcagc actttgc 57

<210> 364
<211> 103
<212> DNA
<213> Homo sapiens

<400> 364
gagcgcaagc ttccgccatc atgtggtggc gcctgtggtg gctgctgctg ctgctgctgc 60

tgctgtggcc catggtgtgg gccagcccca agatggtgca agg 103

<210> 365
<211> 57
<212> DNA
<213> Homo sapiens

<400> 365
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<210> 366
<211> 38
<212> DNA
<213> Homo sapiens

<400> 366
aggagcgtcg acaaaagaag ccccaagatg gtgcaagg 38

<210> 367
<211> 26
<212> DNA

<213> Homo sapiens

<400> 367
ttataagcct aaggcagctt gacttg 26

<210> 368
<211> 115
<212> DNA
<213> Homo sapiens

<400> 368
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tgctgctgct ggccctgtgg gcccccgccc gcggcagccc caagatggtg caagg 115

<210> 369
<211> 57
<212> DNA
<213> Homo sapiens

<400> 369
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<210> 370
<211> 29
<212> DNA
<213> Homo sapiens

<400> 370
gagcgcggat ccaagcttcc gccatcatg 29

<210> 371
<211> 26
<212> DNA
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<400> 371
ctttaaatcg atgagcaacc tcactc 26

<210> 372
<211> 109
<212> DNA
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tgctgctgct gtggcccatg gtgtgggcca gccccaagat ggtgcaagg 109

<210> 373
<211> 38
<212> DNA
<213> Homo sapiens

<400> 373
gtcgtcggta ccttataagc ctaaggcagc ttgacttg 38

<210> 374
<211> 80
<212> DNA
<213> Homo sapiens

<400> 374
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tgctgctgct gtggcccatg 80

<210> 375
<211> 57
<212> DNA
<213> Homo sapiens

<400> 375
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<210> 376
<211> 80
<212> DNA
<213> Homo sapiens

<400> 376
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tgctgctgct gtggcccatg 80

<210> 377
<211> 57
<212> DNA
<213> Homo sapiens

<400> 377
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<210> 378
<211> 40
<212> DNA
<213> Homo sapiens

<400> 378
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<210> 379
<211> 40
<212> DNA
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<400> 379
gcaccgggcg cgccttaatg ccgcctcagc actttgcagc 40

<210> 380
<211> 37
<212> DNA
<213> Homo sapiens

<400> 380
aggagcgtcg acaaaagaag ccccaagatg gtgcaag 37

<210> 381
<211> 56
<212> DNA
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<400> 381
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<210> 382
<211> 103
<212> DNA
<213> Homo sapiens

<400> 382
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tgctgtggcc catggtgtgg gccagcccca agatggtgca agg 103

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<211> 57
<212> DNA
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<400> 383
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<210> 384
<211> 38
<212> DNA
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<400> 384
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<210> 385
<211> 56
<212> DNA
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<400> 385
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<210> 386
<211> 40
<212> DNA
<213> Homo sapiens

<400> 386
aggagcgtcg acaaaagaac caagactgaa tcctcctcac 40

<210> 387
<211> 59

<212> DNA
<213> Homo sapiens

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<210> 388
<211> 56
<212> DNA
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<400> 388
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<210> 389
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<212> DNA
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<210> 390
<211> 40
<212> DNA
<213> Homo sapiens

<400> 390
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<210> 391
<211> 59
<212> DNA
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<400> 391
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<210> 392
<211> 99
<212> DNA
<213> Homo sapiens

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tacaagatcc cgcgtcagag aattatggat tactatgag 99

<210> 393
<211> 59
<212> DNA
<213> Homo sapiens

<400> 393
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<210> 394
<211> 40
<212> DNA
<213> Homo sapiens

<400> 394
aggagcgtcg acaaaagagg accttaccac ccctcagagt 40

<210> 395
<211> 107
<212> DNA
<213> Homo sapiens

<400> 395
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ctccgcctga gccaccgcca ccagagttct ccttcatgtc cttgata 107

<210> 396
<211> 47
<212> DNA
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<400> 396
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<210> 397
<211> 53
<212> DNA
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<400> 397
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<210> 398
<211> 40
<212> DNA
<213> Homo sapiens

<400> 398
aggagcgtcg acaaaagagg accttaccac ccctcagagt 40

<210> 399
<211> 59
<212> DNA
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<400> 399
ctttaaatcg atgagcaacc tcactcttgt gtgcatcgtt ctccttcatg tccttgata 59

<210> 400
<211> 70
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<210> 460
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tccagcggcc tgggctgcaa agtgctgagg cgacat 96

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gggctgaggt tgttt 135

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<212> DNA
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gggctgaggt tgttt 135

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tccagtggcc tgggctgcaa agtgctgagg cggcat 96

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<212> DNA
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cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

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gacaagtggg tccaggacta tatcaaggac atgaaggaga ac 222

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<212> DNA
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tccagtggcc tgggctgcaa agtgctgagg cggcat 96

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<212> DNA
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<213> Homo sapiens

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tccagtggcc tgggctgcaa agtgctgagg cggcat 96

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tccagtggcc tgggctgcaa agtgctgagg cggcat 96

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<213> Canis familiaris

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<210> 483
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<212> DNA
<213> Macaca fascicularis

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tccagcggcc tgggctgcaa agtgctgagg cgacat 96

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gggctgaggt tgttt 135

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gggctgaggt tgttt 135

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<212> DNA
<213> Mus musculus

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aagccttag 249

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ccc 123

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<212> DNA
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ccaggtatcg gtgacccagt tacctgtttg aagtccggtg ctatctgtca cccagtcttc 180

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ccaggtatcg gtgacccagt tacctgtttg aagtccggtg ctatctgtca cccagtcttc 180

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aaaccatag 249

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<212> PRT
<213> Macaca fascicularis

<400> 496

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Leu Gly Ser Gln Ala Ser Pro Lys Met Val Arg Gly Ser Gly Cys Phe
20 25 30

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
35 40 45

Val Leu Arg Arg His Asp Thr His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Glu His Phe Lys Gly Leu Val Leu Val Ala Phe
65 70 75 80

Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Glu His Val Lys Leu Val
85 90 95

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
100 105 110

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
115 120 125

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
130 135 140

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
145 150 155 160

Asp Asn Pro Asn Leu Pro Pro Leu Val Arg Pro Glu Val Asp Val Met
165 170 175

Cys Thr Ala Phe His Asp Asn Glu Ala Thr Phe Leu Lys Lys Tyr Leu
180 185 190

Tyr Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
195 200 205

Phe Phe Ala Ala Arg Tyr Lys Ala Ala Phe Ala Glu Cys Cys Gln Ala

```
    210                 215                 220

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
225                 230                 235                 240

Gln Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
                245                 250                 255

Gln Lys Phe Gly Asp Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
            260                 265                 270

Ser Gln Lys Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
        275                 280                 285

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
    290                 295                 300

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Met Cys Glu Asn
305                 310                 315                 320

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Asp Lys Pro Leu
                325                 330                 335

Leu Glu Lys Ser His Cys Leu Ala Glu Val Glu Asn Asp Glu Met Pro
            340                 345                 350

Ala Asp Leu Pro Ser Leu Ala Ala Asp Tyr Val Glu Ser Lys Asp Val
        355                 360                 365

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
    370                 375                 380

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Met Leu Leu Leu
385                 390                 395                 400

Arg Leu Ala Lys Ala Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Ala
                405                 410                 415

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Gln Pro
            420                 425                 430

Leu Val Glu Glu Pro Gln Asn Leu Val Lys Gln Asn Cys Glu Leu Phe
        435                 440                 445

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
    450                 455                 460
```

```
Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
465                 470                 475                 480

Arg Asn Leu Gly Lys Val Gly Ala Lys Cys Cys Lys Leu Pro Glu Ala
                485                 490                 495

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Arg
            500                 505                 510

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Val Thr Lys
        515                 520                 525

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
    530                 535                 540

Glu Leu Asp Glu Ala Tyr Val Pro Lys Ala Phe Asn Ala Glu Thr Phe
545                 550                 555                 560

Thr Phe His Ala Asp Met Cys Thr Leu Ser Glu Lys Glu Lys Gln Val
                565                 570                 575

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
            580                 585                 590

Thr Lys Glu Gln Leu Lys Gly Val Met Asp Asn Phe Ala Ala Phe Val
        595                 600                 605

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Ala Cys Phe Ala Glu Glu
    610                 615                 620

Gly Pro Lys Phe Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635
```

<210> 497
<211> 653
<212> PRT
<213> Rattus norvegicus

<400> 497

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Ser Gln Asp Ser Ala Phe Arg Ile
            20                  25                  30

Gln Glu Arg Leu Arg Asn Ser Lys Met Ala His Ser Ser Ser Cys Phe
        35                  40                  45
```

```
Gly Gln Lys Ile Asp Arg Ile Gly Ala Val Ser Arg Leu Gly Cys Asp
    50                  55                  60

Gly Leu Arg Leu Phe Glu Ala His Lys Ser Glu Ile Ala His Arg Phe
65                  70                  75                  80

Lys Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe
                85                  90                  95

Ser Gln Tyr Leu Gln Lys Cys Pro Tyr Glu Glu His Ile Lys Leu Val
            100                 105                 110

Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Asn Ala
        115                 120                 125

Glu Asn Cys Asp Lys Ser Ile His Thr Leu Phe Gly Asp Lys Leu Cys
    130                 135                 140

Ala Ile Pro Lys Leu Arg Asp Asn Tyr Gly Glu Leu Ala Asp Cys Cys
145                 150                 155                 160

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
                165                 170                 175

Asp Asn Pro Asn Leu Pro Pro Phe Gln Arg Pro Glu Ala Glu Ala Met
            180                 185                 190

Cys Thr Ser Phe Gln Glu Asn Pro Thr Ser Phe Leu Gly His Tyr Leu
        195                 200                 205

His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
    210                 215                 220

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

Ser Asp Lys Ala Ala Cys Leu Thr Pro Lys Leu Asp Ala Val Lys Glu
                245                 250                 255

Lys Ala Leu Val Ala Ala Val Arg Gln Arg Met Lys Cys Ser Ser Met
            260                 265                 270

Gln Arg Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Met
        275                 280                 285

Ser Gln Arg Phe Pro Asn Ala Glu Phe Ala Glu Ile Thr Lys Leu Ala
    290                 295                 300
```

```
Thr Asp Val Thr Lys Ile Asn Lys Glu Cys Cys His Gly Asp Leu Leu
305                 310                 315                 320

Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn
                325                 330                 335

Gln Ala Thr Ile Ser Ser Lys Leu Gln Ala Cys Cys Asp Lys Pro Val
            340                 345                 350

Leu Gln Lys Ser Gln Cys Leu Ala Glu Thr Glu His Asp Asn Ile Pro
        355                 360                 365

Ala Asp Leu Pro Ser Ile Ala Ala Asp Phe Val Glu Asp Lys Glu Val
    370                 375                 380

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu
385                 390                 395                 400

Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu
                405                 410                 415

Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu
            420                 425                 430

Gly Asp Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro
        435                 440                 445

Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Glu Leu Tyr
    450                 455                 460

Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Val Leu Val Arg Tyr
465                 470                 475                 480

Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala
                485                 490                 495

Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Ala
            500                 505                 510

Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg
        515                 520                 525

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Val Thr Lys
    530                 535                 540

Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu
545                 550                 555                 560
```

```
Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe
                565                 570                 575

Thr Phe His Ser Asp Ile Cys Thr Leu Pro Asp Lys Glu Lys Gln Ile
            580                 585                 590

Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala
        595                 600                 605

Thr Glu Asp Gln Leu Lys Thr Val Met Gly Asp Phe Ala Gln Phe Val
    610                 615                 620

Asp Lys Cys Cys Lys Ala Ala Asp Lys Asp Asn Cys Phe Ala Thr Glu
625                 630                 635                 640

Gly Pro Asn Leu Val Ala Arg Ser Lys Glu Ala Leu Ala
                645                 650
```

<210> 498
<211> 650
<212> PRT
<213> Rattus norvegicus

<400> 498

```
Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1               5                   10                  15

Leu Gly Ser Gln Ala Ser Gln Asp Ser Ala Phe Arg Ile Gln Glu Arg
            20                  25                  30

Leu Arg Asn Ser Lys Met Ala His Ser Ser Ser Cys Phe Gly Gln Lys
        35                  40                  45

Ile Asp Arg Ile Gly Ala Val Ser Arg Leu Gly Cys Asp Gly Leu Arg
    50                  55                  60

Leu Phe Glu Ala His Lys Ser Glu Ile Ala His Arg Phe Lys Asp Leu
65                  70                  75                  80

Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr
                85                  90                  95

Leu Gln Lys Cys Pro Tyr Glu Glu His Ile Lys Leu Val Gln Glu Val
            100                 105                 110

Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Asn Ala Glu Asn Cys
        115                 120                 125
```

```
Asp Lys Ser Ile His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro
    130                 135                 140

Lys Leu Arg Asp Asn Tyr Gly Glu Leu Ala Asp Cys Cys Ala Lys Gln
145                 150                 155                 160

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
                165                 170                 175

Asn Leu Pro Pro Phe Gln Arg Pro Glu Ala Glu Ala Met Cys Thr Ser
            180                 185                 190

Phe Gln Glu Asn Pro Thr Ser Phe Leu Gly His Tyr Leu His Glu Val
        195                 200                 205

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala
    210                 215                 220

Glu Lys Tyr Asn Glu Val Leu Thr Gln Cys Cys Thr Glu Ser Asp Lys
225                 230                 235                 240

Ala Ala Cys Leu Thr Pro Lys Leu Asp Ala Val Lys Glu Lys Ala Leu
                245                 250                 255

Val Ala Ala Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Arg Phe
            260                 265                 270

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Met Ser Gln Arg
        275                 280                 285

Phe Pro Asn Ala Glu Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Val
    290                 295                 300

Thr Lys Ile Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
305                 310                 315                 320

Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr
                325                 330                 335

Ile Ser Ser Lys Leu Gln Ala Cys Cys Asp Lys Pro Val Leu Gln Lys
            340                 345                 350

Ser Gln Cys Leu Ala Glu Thr Glu His Asp Asn Ile Pro Ala Asp Leu
        355                 360                 365

Pro Ser Ile Ala Ala Asp Phe Val Glu Asp Lys Glu Val Cys Lys Asn
```

```
    370                 375                 380

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr
385                 390                 395                 400

Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala
                405                 410                 415

Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Gly Asp Pro
            420                 425                 430

Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu
        435                 440                 445

Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Glu Leu Tyr Glu Lys Leu
    450                 455                 460

Gly Glu Tyr Gly Phe Gln Asn Ala Val Leu Val Arg Tyr Thr Gln Lys
465                 470                 475                 480

Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu
                485                 490                 495

Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Ala Gln Arg Leu
            500                 505                 510

Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Leu Cys Val
        515                 520                 525

Leu His Glu Lys Thr Pro Val Ser Glu Lys Val Thr Lys Cys Cys Ser
    530                 535                 540

Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp
545                 550                 555                 560

Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His
                565                 570                 575

Ser Asp Ile Cys Thr Leu Pro Asp Lys Glu Lys Gln Ile Lys Lys Gln
            580                 585                 590

Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Glu Asp
        595                 600                 605

Gln Leu Lys Thr Val Met Gly Asp Phe Ala Gln Phe Val Asp Lys Cys
    610                 615                 620
```

```
Cys Lys Ala Ala Asp Lys Asp Asn Cys Phe Ala Thr Glu Gly Pro Asn
625                 630                 635                 640

Leu Val Ala Arg Ser Lys Glu Ala Leu Ala
                645                 650

<210>  499
<211>  639
<212>  PRT
<213>  Homo sapiens

<400>  499

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Lys Met Val Gln Gly Ser Gly Cys
            20                  25                  30

Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys
        35                  40                  45

Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg
    50                  55                  60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65                  70                  75                  80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                85                  90                  95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            100                 105                 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        115                 120                 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    130                 135                 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145                 150                 155                 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190
```

```
Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                325                 330                 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                405                 410                 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            420                 425                 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445
```

```
Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    530                 535                 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545                 550                 555                 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                565                 570                 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            580                 585                 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        595                 600                 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    610                 615                 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635


<210>  500
<211>  640
<212>  PRT
<213>  Homo sapiens

<400>  500

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Lys Met Val Gln Gly Ser Gly Cys
            20                  25                  30
```

```
Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys
        35                  40                  45

Lys Val Leu Arg Gly Gly Gly Asp Ala His Lys Ser Glu Val Ala His
    50                  55                  60

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
65                  70                  75                  80

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
                85                  90                  95

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
            100                 105                 110

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
        115                 120                 125

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
    130                 135                 140

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
145                 150                 155                 160

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
                165                 170                 175

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
            180                 185                 190

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
        195                 200                 205

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
    210                 215                 220

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
225                 230                 235                 240

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
                245                 250                 255

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
            260                 265                 270

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
        275                 280                 285
```

```
Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
    290                 295                 300

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
305                 310                 315                 320

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
                325                 330                 335

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
            340                 345                 350

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
        355                 360                 365

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
    370                 375                 380

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
385                 390                 395                 400

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
                405                 410                 415

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
            420                 425                 430

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
        435                 440                 445

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
    450                 455                 460

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
465                 470                 475                 480

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
                485                 490                 495

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
            500                 505                 510

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
        515                 520                 525

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
```

530 535 540

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
545 550 555 560

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
565 570 575

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
580 585 590

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
595 600 605

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala
610 615 620

Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635 640

<210> 501
<211> 638
<212> PRT
<213> Homo sapiens

<400> 501

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln

```
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

```
Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
    610                 615                 620
```

```
Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
625                 630                 635


<210>  502
<211>  774
<212>  PRT
<213>  Homo sapiens

<400>  502

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15


Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30


His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45


Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60


Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80


Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95


Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110


Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125


His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140


Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160


Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175


Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190


Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205
```

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

```
Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
            660                 665                 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
        675                 680                 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
```

705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 503
<211> 667
<212> PRT
<213> Homo sapiens

<400> 503

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys

```
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400
```

```
Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
    610                 615                 620

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Ser Pro
625                 630                 635                 640

Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile
                645                 650                 655
```

Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
660 665

<210> 504
<211> 641
<212> PRT
<213> Homo sapiens

<400> 504

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Arg His Asp Ala His Lys Ser Glu Val Ala
50 55 60

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
65 70 75 80

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
85 90 95

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
100 105 110

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
115 120 125

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
130 135 140

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
145 150 155 160

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
165 170 175

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
180 185 190

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
195 200 205

```
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
    210                 215                 220

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
225                 230                 235                 240

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
                245                 250                 255

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
            260                 265                 270

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
        275                 280                 285

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
    290                 295                 300

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
305                 310                 315                 320

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
                325                 330                 335

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
            340                 345                 350

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
        355                 360                 365

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
    370                 375                 380

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
385                 390                 395                 400

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
                405                 410                 415

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
            420                 425                 430

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
        435                 440                 445

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
    450                 455                 460
```

```
Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
465                 470                 475                 480

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
                485                 490                 495

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
            500                 505                 510

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
        515                 520                 525

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
    530                 535                 540

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
545                 550                 555                 560

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
                565                 570                 575

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
            580                 585                 590

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
        595                 600                 605

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
    610                 615                 620

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
625                 630                 635                 640

Leu
```

<210> 505
<211> 639
<212> PRT
<213> Homo sapiens

<400> 505

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30
```

```
His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
```

```
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525
```

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
610 615 620

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg
625 630 635

<210> 506
<211> 640
<212> PRT
<213> Homo sapiens

<400> 506

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

```
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

```
Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
    610                 615                 620
```

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg
625 630 635 640

<210> 507
<211> 635
<212> PRT
<213> Homo sapiens

<400> 507

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys
20 25 30

Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg
35 40 45

Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
50 55 60

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
65 70 75 80

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
85 90 95

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
100 105 110

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
115 120 125

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
130 135 140

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
145 150 155 160

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
165 170 175

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
180 185 190

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
195 200 205

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
210 215 220

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
225 230 235 240

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
245 250 255

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
260 265 270

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
275 280 285

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
290 295 300

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
305 310 315 320

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
325 330 335

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
340 345 350

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
355 360 365

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
370 375 380

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
385 390 395 400

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
405 410 415

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
420 425 430

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
435 440 445

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys

```
    450                 455                 460

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
465                 470                 475                 480

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
                485                 490                 495

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
            500                 505                 510

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
        515                 520                 525

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
    530                 535                 540

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
545                 550                 555                 560

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
                565                 570                 575

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
            580                 585                 590

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
        595                 600                 605

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
    610                 615                 620

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635


<210>  508
<211>  636
<212>  PRT
<213>  Homo sapiens

<400>  508

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg
            20                  25                  30

Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
```

```
        35                  40                  45

Arg Arg His Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
    50                  55                  60

Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
65                  70                  75                  80

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
                85                  90                  95

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
            100                 105                 110

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
        115                 120                 125

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
    130                 135                 140

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
145                 150                 155                 160

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
                165                 170                 175

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
            180                 185                 190

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
        195                 200                 205

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
    210                 215                 220

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
225                 230                 235                 240

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
                245                 250                 255

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
            260                 265                 270

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
        275                 280                 285
```

```
Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
    290                 295                 300

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
305                 310                 315                 320

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
                325                 330                 335

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
            340                 345                 350

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
        355                 360                 365

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
    370                 375                 380

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
385                 390                 395                 400

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
                405                 410                 415

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
            420                 425                 430

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
        435                 440                 445

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
    450                 455                 460

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
465                 470                 475                 480

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
                485                 490                 495

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
            500                 505                 510

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
        515                 520                 525

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
    530                 535                 540
```

```
Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
545                 550                 555                 560

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
                565                 570                 575

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
            580                 585                 590

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
        595                 600                 605

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
    610                 615                 620

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635
```

<210> 509
<211> 678
<212> PRT
<213> Homo sapiens

<400> 509

```
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
            20                  25                  30

Ser Ala Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
        35                  40                  45

Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
    50                  55                  60

Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65                  70                  75                  80

Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn Asp Ala His
                85                  90                  95

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
            100                 105                 110

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
        115                 120                 125
```

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
130 135 140

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
145 150 155 160

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
165 170 175

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
180 185 190

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
195 200 205

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
210 215 220

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
225 230 235 240

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
245 250 255

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
260 265 270

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
275 280 285

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
290 295 300

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
305 310 315 320

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
325 330 335

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
340 345 350

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
355 360 365

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
370 375 380

```
Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
385                 390                 395                 400

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
                405                 410                 415

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
            420                 425                 430

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
        435                 440                 445

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
    450                 455                 460

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
465                 470                 475                 480

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
                485                 490                 495

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
            500                 505                 510

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
        515                 520                 525

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
    530                 535                 540

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
545                 550                 555                 560

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
                565                 570                 575

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
            580                 585                 590

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
        595                 600                 605

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
    610                 615                 620

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
```

625 630 635 640

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
645 650 655

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
660 665 670

Gln Ala Ala Leu Gly Leu
675

<210> 510
<211> 639
<212> PRT
<213> Homo sapiens

<400> 510

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Asp Ala His Lys Ser Glu Val Ala His Arg
50 55 60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65 70 75 80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
85 90 95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
100 105 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
115 120 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
130 135 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145 150 155 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val

```
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                325                 330                 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                405                 410                 415
```

```
Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            420                 425                 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    530                 535                 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545                 550                 555                 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                565                 570                 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            580                 585                 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        595                 600                 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    610                 615                 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635
```

<210> 511
<211> 655
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (274)..(274)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 511

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Asp Ala His Lys Ser Glu Val Ala His Arg
50 55 60

Phe Lys Asp Leu Gly Glu Asp Ala His Lys Ser Glu Val Ala His Arg
65 70 75 80

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
85 90 95

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
100 105 110

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
115 120 125

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
130 135 140

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
145 150 155 160

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
165 170 175

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
180 185 190

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
195 200 205

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
210 215 220

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln

225 230 235 240

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
245 250 255

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
260 265 270

Leu Xaa Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
275 280 285

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
290 295 300

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
305 310 315 320

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
325 330 335

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
340 345 350

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
355 360 365

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
370 375 380

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
385 390 395 400

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
405 410 415

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
420 425 430

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
435 440 445

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
450 455 460

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
465 470 475 480

```
Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
                485                 490                 495

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
            500                 505                 510

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
        515                 520                 525

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
    530                 535                 540

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
545                 550                 555                 560

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
                565                 570                 575

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
            580                 585                 590

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
        595                 600                 605

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
    610                 615                 620

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
625                 630                 635                 640

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                645                 650                 655


<210>  512
<211>  671
<212>  PRT
<213>  Homo sapiens

<400>  512

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Pro Lys Met Val Gln Gly Ser
            20                  25                  30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
        35                  40                  45
```

```
Gly Cys Lys Val Leu Arg Asp Ala His Lys Ser Glu Val Ala His Arg
    50                  55                  60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65                  70                  75                  80

Phe Ala Gln Tyr Leu Gln Asp Ala His Lys Ser Glu Val Ala His Arg
                85                  90                  95

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
            100                 105                 110

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
        115                 120                 125

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
    130                 135                 140

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
145                 150                 155                 160

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
                165                 170                 175

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
            180                 185                 190

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
        195                 200                 205

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
    210                 215                 220

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
225                 230                 235                 240

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
                245                 250                 255

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
            260                 265                 270

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
        275                 280                 285

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
    290                 295                 300
```

```
Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
305                 310                 315                 320

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
                325                 330                 335

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
            340                 345                 350

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
        355                 360                 365

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
    370                 375                 380

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
385                 390                 395                 400

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
                405                 410                 415

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
            420                 425                 430

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
        435                 440                 445

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
    450                 455                 460

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
465                 470                 475                 480

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
                485                 490                 495

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
            500                 505                 510

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
        515                 520                 525

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
    530                 535                 540

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
545                 550                 555                 560
```

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
565 570 575

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
580 585 590

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
595 600 605

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
610 615 620

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
625 630 635 640

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
645 650 655

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
660 665 670

<210> 513
<211> 638
<212> PRT
<213> Homo sapiens

<400> 513

Met Lys Val Ser Val Ala Ala Leu Ser Cys Leu Met Leu Val Thr Ala
1 5 10 15

Leu Gly Ser Gln Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe
20 25 30

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
35 40 45

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
50 55 60

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
65 70 75 80

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
85 90 95

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
100 105 110

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
115 120 125

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
130 135 140

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
145 150 155 160

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
165 170 175

Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
180 185 190

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
195 200 205

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
210 215 220

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
225 230 235 240

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
245 250 255

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
260 265 270

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
275 280 285

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
290 295 300

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
305 310 315 320

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
325 330 335

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
340 345 350

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu

```
        355                 360                 365

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
    370                 375                 380

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
385                 390                 395                 400

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
                405                 410                 415

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
            420                 425                 430

Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
        435                 440                 445

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
    450                 455                 460

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
465                 470                 475                 480

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
                485                 490                 495

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
            500                 505                 510

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
        515                 520                 525

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
    530                 535                 540

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
545                 550                 555                 560

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
                565                 570                 575

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
            580                 585                 590

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Ser Pro
        595                 600                 605
```

Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile
610 615 620

Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
625 630 635

<210> 514
<211> 638
<212> PRT
<213> Homo sapiens

<400> 514

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

```
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
```

```
Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
    610                 615                 620

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
625                 630                 635


<210>  515
<211>  639
<212>  PRT
<213>  Homo sapiens

<400>  515

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Gly Ser Leu Asp Lys Arg Ser Ala Lys Met Val Gln Gly Ser
            20                  25                  30
```

```
Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
        35                  40                  45

Gly Cys Lys Val Leu Arg Asp Ala His Lys Ser Glu Val Ala His Arg
    50                  55                  60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65                  70                  75                  80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                85                  90                  95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            100                 105                 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        115                 120                 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    130                 135                 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145                 150                 155                 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285
```

```
Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                325                 330                 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                405                 410                 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            420                 425                 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
```

530 535 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545 550 555 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
565 570 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
580 585 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
595 600 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
610 615 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 516
<211> 639
<212> PRT
<213> Homo sapiens

<400> 516

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg Ser Leu Lys Met Val Gln Gly Ser
20 25 30

Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu
35 40 45

Gly Cys Lys Val Leu Arg Asp Ala His Lys Ser Glu Val Ala His Arg
50 55 60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65 70 75 80

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
85 90 95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
100 105 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu

```
        115                 120                 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    130                 135                 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145                 150                 155                 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
                325                 330                 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365
```

```
Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                405                 410                 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            420                 425                 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    530                 535                 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545                 550                 555                 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                565                 570                 575

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            580                 585                 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        595                 600                 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    610                 615                 620
```

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 517
<211> 640
<212> PRT
<213> Canis familiaris

<400> 517

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Gly Ser Leu Asp Lys Arg Glu Ala Tyr Lys Ser Glu Ile Ala
20 25 30

His Arg Tyr Asn Asp Leu Gly Glu Glu His Phe Arg Gly Leu Val Leu
35 40 45

Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Ala Lys Glu Val Thr Glu Phe Ala Lys Ala Cys Ala Ala Glu
65 70 75 80

Glu Ser Gly Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Ser Leu Arg Asp Lys Tyr Gly Asp Met Ala
100 105 110

Asp Cys Cys Glu Lys Gln Glu Pro Asp Arg Asn Glu Cys Phe Leu Ala
115 120 125

His Lys Asp Asp Asn Pro Gly Phe Pro Pro Leu Val Ala Pro Glu Pro
130 135 140

Asp Ala Leu Cys Ala Ala Phe Gln Asp Asn Glu Gln Leu Phe Leu Gly
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Tyr Tyr Ala Gln Gln Tyr Lys Gly Val Phe Ala Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Gly Pro Lys Ile Glu Ala
195 200 205

Leu Arg Glu Lys Val Leu Leu Ser Ser Ala Lys Glu Arg Phe Lys Cys
210 215 220

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

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Asp Phe Ala Glu Ile Ser
245 250 255

Lys Val Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Met
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Thr Lys Leu Lys Glu Cys Cys Asp
290 295 300

Lys Pro Val Leu Glu Lys Ser Gln Cys Leu Ala Glu Val Glu Arg Asp
305 310 315 320

Glu Leu Pro Gly Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Asp
325 330 335

Lys Glu Val Cys Lys Asn Tyr Gln Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Thr Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Glu Tyr Ser Val Ser
355 360 365

Leu Leu Leu Arg Leu Ala Lys Glu Tyr Glu Ala Thr Leu Glu Lys Cys
370 375 380

Cys Ala Thr Asp Asp Pro Pro Thr Cys Tyr Ala Lys Val Leu Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Asp Glu Pro Gln Asn Leu Val Lys Thr Asn Cys
405 410 415

Glu Leu Phe Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Lys Leu Gly Lys Val Gly Thr Lys Cys Cys Lys Lys
450 455 460

```
Pro Glu Ser Glu Arg Met Ser Cys Ala Glu Asp Phe Leu Ser Val Val
465                 470                 475                 480

Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Arg
                485                 490                 495

Val Thr Lys Cys Cys Ser Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Gly Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Leu Cys Thr Leu Pro Glu Ala Glu
    530                 535                 540

Lys Gln Val Lys Lys Gln Thr Ala Leu Val Glu Leu Leu Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Asp Glu Gln Leu Lys Thr Val Met Gly Asp Phe Gly
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Ala Ala Glu Asn Lys Glu Gly Cys Phe
            580                 585                 590

Ser Glu Glu Gly Pro Lys Leu Val Ala Ala Ala Gln Ala Ala Leu Val
        595                 600                 605

Ser Pro Lys Met Met His Lys Ser Gly Cys Phe Gly Arg Arg Leu Asp
    610                 615                 620

Arg Ile Gly Ser Leu Ser Gly Leu Gly Cys Asn Val Leu Arg Lys Tyr
625                 630                 635                 640
```

<210> 518
<211> 637
<212> PRT
<213> Canis familiaris

<400> 518

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Gly Ser Leu Asp Lys Arg Glu Ala Tyr Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Tyr Asn Asp Leu Gly Glu Glu His Phe Arg Gly Leu Val Leu
        35                  40                  45
```

```
Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Ala Lys Glu Val Thr Glu Phe Ala Lys Ala Cys Ala Ala Glu
65                  70                  75                  80

Glu Ser Gly Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Ser Leu Arg Asp Lys Tyr Gly Asp Met Ala
            100                 105                 110

Asp Cys Cys Glu Lys Gln Glu Pro Asp Arg Asn Glu Cys Phe Leu Ala
        115                 120                 125

His Lys Asp Asp Asn Pro Gly Phe Pro Pro Leu Val Ala Pro Glu Pro
    130                 135                 140

Asp Ala Leu Cys Ala Ala Phe Gln Asp Asn Glu Gln Leu Phe Leu Gly
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Gln Gln Tyr Lys Gly Val Phe Ala Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Gly Pro Lys Ile Glu Ala
        195                 200                 205

Leu Arg Glu Lys Val Leu Leu Ser Ser Ala Lys Glu Arg Phe Lys Cys
    210                 215                 220

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

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Asp Phe Ala Glu Ile Ser
                245                 250                 255

Lys Val Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Thr Lys Leu Lys Glu Cys Cys Asp
```

```
    290                 295                 300

Lys Pro Val Leu Glu Lys Ser Gln Cys Leu Ala Glu Val Glu Arg Asp
305                 310                 315                 320

Glu Leu Pro Gly Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Asp
                325                 330                 335

Lys Glu Val Cys Lys Asn Tyr Gln Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Glu Tyr Ser Val Ser
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Glu Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Thr Asp Asp Pro Pro Thr Cys Tyr Ala Lys Val Leu Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Asp Glu Pro Gln Asn Leu Val Lys Thr Asn Cys
                405                 410                 415

Glu Leu Phe Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Lys Leu Gly Lys Val Gly Thr Lys Cys Cys Lys Lys
    450                 455                 460

Pro Glu Ser Glu Arg Met Ser Cys Ala Glu Asp Phe Leu Ser Val Val
465                 470                 475                 480

Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Arg
                485                 490                 495

Val Thr Lys Cys Cys Ser Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Gly Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Leu Cys Thr Leu Pro Glu Ala Glu
    530                 535                 540
```

```
Lys Gln Val Lys Lys Gln Thr Ala Leu Val Glu Leu Leu Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Asp Glu Gln Leu Lys Thr Val Met Gly Asp Phe Gly
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Ala Ala Glu Asn Lys Glu Gly Cys Phe
            580                 585                 590

Ser Glu Glu Gly Pro Lys Leu Val Ala Ala Ala Gln Ala Ala Leu Val
        595                 600                 605

Ser Pro Lys Met Met His Lys Ser Gly Cys Phe Gly Arg Arg Leu Asp
    610                 615                 620

Arg Ile Gly Ser Leu Ser Gly Leu Gly Cys Asn Val Leu
625                 630                 635


<210>  519
<211>  642
<212>  PRT
<213>  Macaca fascicularis

<400>  519

Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1               5                   10                  15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Asp Thr His
            20                  25                  30

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu His Phe
        35                  40                  45

Lys Gly Leu Val Leu Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro
    50                  55                  60

Phe Glu Glu His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
65                  70                  75                  80

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
                85                  90                  95

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
            100                 105                 110

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
        115                 120                 125
```

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Pro Leu
130 135 140

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
145 150 155 160

Ala Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Val Ala Arg Arg His Pro
165 170 175

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Ala Arg Tyr Lys Ala
180 185 190

Ala Phe Ala Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
195 200 205

Pro Lys Leu Asp Glu Leu Arg Asp Gln Gly Lys Ala Ser Ser Ala Lys
210 215 220

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Asp Arg Ala Phe
225 230 235 240

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Lys Phe Pro Lys Ala Glu
245 250 255

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
260 265 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
275 280 285

Leu Ala Lys Tyr Met Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
290 295 300

Lys Glu Cys Cys Asp Lys Pro Leu Leu Glu Lys Ser His Cys Leu Ala
305 310 315 320

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
325 330 335

Asp Tyr Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
340 345 350

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
355 360 365

Asp Tyr Ser Val Met Leu Leu Leu Arg Leu Ala Lys Ala Tyr Glu Ala
370 375 380

```
Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
385                 390                 395                 400

Lys Val Phe Asp Glu Phe Gln Pro Leu Val Glu Glu Pro Gln Asn Leu
                405                 410                 415

Val Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
            420                 425                 430

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
        435                 440                 445

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ala
    450                 455                 460

Lys Cys Cys Lys Leu Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
465                 470                 475                 480

Tyr Leu Ser Val Val Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr
                485                 490                 495

Pro Val Ser Glu Lys Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
            500                 505                 510

Arg Arg Pro Cys Phe Ser Ala Leu Glu Leu Asp Glu Ala Tyr Val Pro
        515                 520                 525

Lys Ala Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Met Cys Thr
    530                 535                 540

Leu Ser Glu Lys Glu Lys Gln Val Lys Lys Gln Thr Ala Leu Val Glu
545                 550                 555                 560

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Gly Val
                565                 570                 575

Met Asp Asn Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
            580                 585                 590

Lys Glu Ala Cys Phe Ala Glu Glu Gly Pro Lys Phe Val Ala Ala Ser
        595                 600                 605

Gln Ala Ala Leu Ala Ser Pro Lys Met Val Arg Gly Ser Gly Cys Phe
    610                 615                 620

Gly Arg Lys Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys
625                 630                 635                 640
```

Val Leu

<210> 520
<211> 658
<212> PRT
<213> Rattus norvegicus

<220>
<221> SITE
<222> (551)..(551)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 520

Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1 5 10 15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Glu Ala His
20 25 30

Lys Ser Glu Ile Ala His Arg Phe Lys Asp Leu Gly Glu Gln His Phe
35 40 45

Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Pro
50 55 60

Tyr Glu Glu His Ile Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys
65 70 75 80

Thr Cys Val Ala Asp Glu Asn Ala Glu Asn Cys Asp Lys Ser Ile His
85 90 95

Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Lys Leu Arg Asp Asn
100 105 110

Tyr Gly Glu Leu Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
115 120 125

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Pro Phe
130 135 140

Gln Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Gln Glu Asn Pro
145 150 155 160

Thr Ser Phe Leu Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro
165 170 175

```
Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Lys Tyr Asn Glu
            180                 185                 190

Val Leu Thr Gln Cys Cys Thr Glu Ser Asp Lys Ala Ala Cys Leu Thr
        195                 200                 205

Pro Lys Leu Asp Ala Val Lys Glu Lys Ala Leu Val Ala Ala Val Arg
    210                 215                 220

Gln Arg Met Lys Cys Ser Ser Met Gln Arg Phe Gly Glu Arg Ala Phe
225                 230                 235                 240

Lys Ala Trp Ala Val Ala Arg Met Ser Gln Arg Phe Pro Asn Ala Glu
                245                 250                 255

Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Val Thr Lys Ile Asn Lys
            260                 265                 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu
        275                 280                 285

Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu
    290                 295                 300

Gln Ala Cys Cys Asp Lys Pro Val Leu Gln Lys Ser Gln Cys Leu Ala
305                 310                 315                 320

Glu Thr Glu His Asp Asn Ile Pro Ala Asp Leu Pro Ser Ile Ala Ala
                325                 330                 335

Asp Phe Val Glu Asp Lys Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
            340                 345                 350

Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro
        355                 360                 365

Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala
    370                 375                 380

Thr Leu Glu Lys Cys Cys Ala Glu Gly Asp Pro Pro Ala Cys Tyr Gly
385                 390                 395                 400

Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu
                405                 410                 415

Val Lys Thr Asn Cys Glu Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe
            420                 425                 430
```

Gln Asn Ala Val Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser
435 440 445

Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr
450 455 460

Lys Cys Cys Thr Leu Pro Glu Ala Gln Arg Leu Pro Cys Val Glu Asp
465 470 475 480

Tyr Leu Ser Ala Ile Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr
485 490 495

Pro Val Ser Glu Lys Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu
500 505 510

Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro
515 520 525

Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
530 535 540

Leu Pro Asp Lys Glu Lys Xaa Ile Lys Lys Gln Thr Ala Leu Ala Glu
545 550 555 560

Leu Val Lys His Lys Pro Lys Ala Thr Glu Asp Gln Leu Lys Thr Val
565 570 575

Met Gly Asp Phe Ala Gln Phe Val Asp Lys Cys Cys Lys Ala Ala Asp
580 585 590

Lys Asp Asn Cys Phe Ala Thr Glu Gly Pro Asn Leu Val Ala Arg Ser
595 600 605

Lys Glu Ala Leu Ala Ser Gln Asp Ser Ala Phe Arg Ile Gln Glu Arg
610 615 620

Leu Arg Asn Ser Lys Met Ala His Ser Ser Ser Cys Phe Gly Gln Lys
625 630 635 640

Ile Asp Arg Ile Gly Ala Val Ser Arg Leu Gly Cys Asp Gly Leu Arg
645 650 655

Leu Phe

<210> 521
<211> 642

<212> PRT
<213> Rattus norvegicus

<400> 521

```
Met Asn Ile Phe Tyr Ile Phe Leu Phe Leu Leu Ser Phe Val Gln Gly
1               5                   10                  15

Leu Glu His Thr His Arg Arg Gly Ser Leu Asp Lys Arg Glu Ala His
            20                  25                  30

Lys Ser Glu Ile Ala His Arg Phe Lys Asp Leu Gly Glu Gln His Phe
        35                  40                  45

Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Pro
    50                  55                  60

Tyr Glu Glu His Ile Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys
65                  70                  75                  80

Thr Cys Val Ala Asp Glu Asn Ala Glu Asn Cys Asp Lys Ser Ile His
                85                  90                  95

Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Lys Leu Arg Asp Asn
            100                 105                 110

Tyr Gly Glu Leu Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
        115                 120                 125

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Pro Phe
    130                 135                 140

Gln Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Gln Glu Asn Pro
145                 150                 155                 160

Thr Ser Phe Leu Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro
                165                 170                 175

Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Lys Tyr Asn Glu
            180                 185                 190

Val Leu Thr Gln Cys Cys Thr Glu Ser Asp Lys Ala Ala Cys Leu Thr
        195                 200                 205

Pro Lys Leu Asp Ala Val Lys Glu Lys Ala Leu Val Ala Ala Val Arg
    210                 215                 220

Gln Arg Met Lys Cys Ser Ser Met Gln Arg Phe Gly Glu Arg Ala Phe
225                 230                 235                 240
```

```
Lys Ala Trp Ala Val Ala Arg Met Ser Gln Arg Phe Pro Asn Ala Glu
                245                 250                 255

Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp Val Thr Lys Ile Asn Lys
            260                 265                 270

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu
        275                 280                 285

Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu
    290                 295                 300

Gln Ala Cys Cys Asp Lys Pro Val Leu Gln Lys Ser Gln Cys Leu Ala
305                 310                 315                 320

Glu Thr Glu His Asp Asn Ile Pro Ala Asp Leu Pro Ser Ile Ala Ala
                325                 330                 335

Asp Phe Val Glu Asp Lys Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
            340                 345                 350

Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro
        355                 360                 365

Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala
    370                 375                 380

Thr Leu Glu Lys Cys Cys Ala Glu Gly Asp Pro Pro Ala Cys Tyr Gly
385                 390                 395                 400

Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu
                405                 410                 415

Val Lys Thr Asn Cys Glu Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe
            420                 425                 430

Gln Asn Ala Val Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser
        435                 440                 445

Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr
    450                 455                 460

Lys Cys Cys Thr Leu Pro Glu Ala Gln Arg Leu Pro Cys Val Glu Asp
465                 470                 475                 480

Tyr Leu Ser Ala Ile Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr
```

485 490 495

Pro Val Ser Glu Lys Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu
500 505 510

Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro
515 520 525

Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
530 535 540

Leu Pro Asp Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu
545 550 555 560

Leu Val Lys His Lys Pro Lys Ala Thr Glu Asp Gln Leu Lys Thr Val
565 570 575

Met Gly Asp Phe Ala Gln Phe Val Asp Lys Cys Cys Lys Ala Ala Asp
580 585 590

Lys Asp Asn Cys Phe Ala Thr Glu Gly Pro Asn Leu Val Ala Arg Ser
595 600 605

Lys Glu Ala Leu Ala Asn Ser Lys Met Ala His Ser Ser Ser Cys Phe
610 615 620

Gly Gln Lys Ile Asp Arg Ile Gly Ala Val Ser Arg Leu Gly Cys Asp
625 630 635 640

Gly Leu

<210> 522
<211> 648
<212> PRT
<213> Mus musculus

<400> 522

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp
20 25 30

Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln
35 40 45

Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu

```
    50                  55                  60

Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn
65                  70                  75                  80

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile
                85                  90                  95

Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys
            100                 105                 110

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
        115                 120                 125

Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr
    130                 135                 140

Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu
145                 150                 155                 160

Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr
                165                 170                 175

Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
            180                 185                 190

Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala
        195                 200                 205

Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys
    210                 215                 220

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
225                 230                 235                 240

Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala Thr Asp
                245                 250                 255

Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys
            260                 265                 270

Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala
        275                 280                 285

Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys
    290                 295                 300
```

```
Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp
305                 310                 315                 320

Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys
                325                 330                 335

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu
            340                 345                 350

Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu
        355                 360                 365

Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn
    370                 375                 380

Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val
385                 390                 395                 400

Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys
                405                 410                 415

Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
            420                 425                 430

Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn
        435                 440                 445

Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg
    450                 455                 460

Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val Cys
465                 470                 475                 480

Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys Cys Cys
                485                 490                 495

Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala Leu Thr Val
            500                 505                 510

Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe
        515                 520                 525

His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys
    530                 535                 540

Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala
545                 550                 555                 560
```

Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr
565 570 575

Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro
580 585 590

Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala Ser Gln Gly Ser Thr
595 600 605

Leu Arg Val Gln Gln Arg Pro Gln Asn Ser Lys Val Thr His Ile Ser
610 615 620

Ser Cys Phe Gly His Lys Ile Asp Arg Ile Gly Ser Val Ser Arg Leu
625 630 635 640

Gly Cys Asn Ala Leu Lys Leu Leu
645

<210> 523
<211> 691
<212> PRT
<213> Homo sapiens

<400> 523

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

```
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380
```

```
Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys
    610                 615                 620

His Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly
```

625 630 635 640

Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro Gly Ile Gly Asp Pro Val
645 650 655

Thr Cys Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg
660 665 670

Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys
675 680 685

Lys Lys Pro
690

<210> 524
<211> 666
<212> PRT
<213> Homo sapiens

<400> 524

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ser Leu Arg Arg Ser Ser Cys Phe
20 25 30

Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn
35 40 45

Ser Phe Arg Tyr Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
50 55 60

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
65 70 75 80

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
85 90 95

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
100 105 110

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
115 120 125

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
130 135 140

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp

```
145                 150                 155                 160

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
                165                 170                 175

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
            180                 185                 190

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
        195                 200                 205

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
    210                 215                 220

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
225                 230                 235                 240

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
                245                 250                 255

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
            260                 265                 270

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
        275                 280                 285

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
    290                 295                 300

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
305                 310                 315                 320

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
                325                 330                 335

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
            340                 345                 350

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
        355                 360                 365

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
    370                 375                 380

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
385                 390                 395                 400
```

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
405 410 415

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
420 425 430

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
435 440 445

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
450 455 460

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
465 470 475 480

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
485 490 495

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
500 505 510

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
515 520 525

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
530 535 540

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
545 550 555 560

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
565 570 575

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
580 585 590

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
595 600 605

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
610 615 620

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Ser Pro Lys
625 630 635 640

Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser
645 650 655

Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
660 665

<210> 525
<211> 650
<212> PRT
<213> Homo sapiens

<400> 525

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

```
Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460
```

```
Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys
    610                 615                 620

His Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly
625                 630                 635                 640

Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro
                645                 650
```

<210> 526
<211> 648
<212> PRT
<213> Homo sapiens

<400> 526

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Gly Ile Gly Asp Pro Val Thr Cys
            20                  25                  30
```

```
Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg Tyr
        35                  40                  45

Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys Lys
    50                  55                  60

Pro Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
65                  70                  75                  80

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
                85                  90                  95

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
            100                 105                 110

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
        115                 120                 125

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
    130                 135                 140

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
145                 150                 155                 160

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
                165                 170                 175

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
            180                 185                 190

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
        195                 200                 205

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
    210                 215                 220

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
225                 230                 235                 240

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
                245                 250                 255

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
            260                 265                 270

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
```

```
        275                 280                 285

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
    290                 295                 300

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
305                 310                 315                 320

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
                325                 330                 335

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
            340                 345                 350

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
        355                 360                 365

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
    370                 375                 380

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
385                 390                 395                 400

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
                405                 410                 415

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
            420                 425                 430

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
        435                 440                 445

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
    450                 455                 460

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
465                 470                 475                 480

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
                485                 490                 495

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
            500                 505                 510

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
        515                 520                 525
```

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
530 535 540

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
545 550 555 560

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
565 570 575

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
580 585 590

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
595 600 605

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
610 615 620

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
625 630 635 640

Val Ala Ala Ser Gln Ala Ala Leu
645

<210> 527
<211> 689
<212> PRT
<213> Homo sapiens

<400> 527

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Gly Ile Gly Asp Pro Val Thr Cys
20 25 30

Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg Tyr
35 40 45

Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys Lys
50 55 60

Pro Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys
65 70 75 80

His Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly
85 90 95

```
Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro Asp Ala His Lys Ser Glu
            100                 105                 110

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
        115                 120                 125

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
    130                 135                 140

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
145                 150                 155                 160

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
                165                 170                 175

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
            180                 185                 190

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
        195                 200                 205

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
    210                 215                 220

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
225                 230                 235                 240

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
                245                 250                 255

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
            260                 265                 270

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
        275                 280                 285

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
    290                 295                 300

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
305                 310                 315                 320

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
                325                 330                 335

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
            340                 345                 350
```

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
355 360 365

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
370 375 380

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
385 390 395 400

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
405 410 415

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
420 425 430

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
435 440 445

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
450 455 460

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
465 470 475 480

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
485 490 495

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
500 505 510

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
515 520 525

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
530 535 540

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
545 550 555 560

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
565 570 575

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
580 585 590

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
595 600 605

```
Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
    610                 615                 620

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
625                 630                 635                 640

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
                645                 650                 655

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
            660                 665                 670

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
        675                 680                 685

Leu
```

<210> 528
<211> 691
<212> PRT
<213> Homo sapiens

<400> 528

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Ile Gly Asp Pro Val Thr Cys
            20                  25                  30

Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg Tyr
        35                  40                  45

Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys Lys
    50                  55                  60

Pro Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys
65                  70                  75                  80

His Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly
                85                  90                  95

Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro Asp Ala His Lys Ser Glu
            100                 105                 110

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
        115                 120                 125
```

```
Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
    130                 135                 140

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
145                 150                 155                 160

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
                165                 170                 175

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
            180                 185                 190

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
        195                 200                 205

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
    210                 215                 220

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
225                 230                 235                 240

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
                245                 250                 255

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
            260                 265                 270

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
        275                 280                 285

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
    290                 295                 300

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
305                 310                 315                 320

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
                325                 330                 335

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
            340                 345                 350

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
        355                 360                 365

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
```

```
    370                 375                 380

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
385                 390                 395                 400

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
                405                 410                 415

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
            420                 425                 430

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
        435                 440                 445

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
    450                 455                 460

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
465                 470                 475                 480

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
                485                 490                 495

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
            500                 505                 510

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
        515                 520                 525

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
    530                 535                 540

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
545                 550                 555                 560

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
                565                 570                 575

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
            580                 585                 590

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
        595                 600                 605

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
    610                 615                 620
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```
Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
625                 630                 635                 640

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
                645                 650                 655

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
            660                 665                 670

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
        675                 680                 685

Leu Gly Leu
    690
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<210> 529
<211> 650
<212> PRT
<213> Homo sapiens

<400> 529

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Ile Gly Asp Pro Val Thr Cys
            20                  25                  30

Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg Tyr
        35                  40                  45

Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys Lys
    50                  55                  60

Pro Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
65                  70                  75                  80

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
                85                  90                  95

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
            100                 105                 110

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
        115                 120                 125

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
    130                 135                 140
```

```
Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
145                 150                 155                 160

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
                165                 170                 175

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
            180                 185                 190

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
        195                 200                 205

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
    210                 215                 220

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
225                 230                 235                 240

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
                245                 250                 255

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
            260                 265                 270

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
        275                 280                 285

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
    290                 295                 300

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
305                 310                 315                 320

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
                325                 330                 335

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
            340                 345                 350

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
        355                 360                 365

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
    370                 375                 380

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
385                 390                 395                 400
```

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
405 410 415

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
420 425 430

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
435 440 445

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
450 455 460

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
465 470 475 480

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
485 490 495

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
500 505 510

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
515 520 525

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
530 535 540

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
545 550 555 560

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
565 570 575

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
580 585 590

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
595 600 605

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
610 615 620

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
625 630 635 640

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
645 650

<210> 530
<211> 650
<212> PRT
<213> Homo sapiens

<400> 530

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

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Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
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465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys
    610                 615                 620

His Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly
625                 630                 635                 640

Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro
                645                 650


<210>  531
<211>  691
<212>  PRT
<213>  Homo sapiens

<400>  531

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
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        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285
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Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540
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Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys
610 615 620

His Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly
625 630 635 640

Leu Pro Gly Thr Lys Cys Cys Lys Lys Pro Gly Ile Gly Asp Pro Val
645 650 655

Thr Cys Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg
660 665 670

Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys
675 680 685

Lys Lys Pro
690

<210> 532
<211> 32
<212> PRT
<213> Macaca fascicularis

<400> 532

Ser Pro Lys Met Val Arg Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 533
<211> 45
<212> PRT
<213> Rattus norvegicus

<400> 533

Ser Gln Asp Ser Ala Phe Arg Ile Gln Glu Arg Leu Arg Asn Ser Lys
1 5 10 15

Met Ala His Ser Ser Ser Cys Phe Gly Gln Lys Ile Asp Arg Ile Gly
20 25 30

Ala Val Ser Arg Leu Gly Cys Asp Gly Leu Arg Leu Phe
35 40 45

<210> 534
<211> 45
<212> PRT
<213> Rattus norvegicus

<400> 534

Ser Gln Asp Ser Ala Phe Arg Ile Gln Glu Arg Leu Arg Asn Ser Lys
1 5 10 15

Met Ala His Ser Ser Ser Cys Phe Gly Gln Lys Ile Asp Arg Ile Gly
20 25 30

Ala Val Ser Arg Leu Gly Cys Asp Gly Leu Arg Leu Phe
35 40 45

<210> 535
<211> 32
<212> PRT
<213> Homo sapiens

<400> 535

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 536
<211> 32
<212> PRT
<213> Homo sapiens

<400> 536

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 537
<211> 32

<212> PRT
<213> Homo sapiens

<400> 537

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 538
<211> 165
<212> PRT
<213> Homo sapiens

<400> 538

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 539
<211> 58
<212> PRT
<213> Homo sapiens

<400> 539

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Ser Pro Lys
20 25 30

Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp Arg Ile Ser
35 40 45

Ser Ser Ser Gly Leu Gly Cys Lys Val Leu
50 55

<210> 540
<211> 32
<212> PRT
<213> Homo sapiens

<400> 540

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 541
<211> 32
<212> PRT
<213> Homo sapiens

<400> 541

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 542
<211> 32
<212> PRT
<213> Homo sapiens

<400> 542

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 543
<211> 32
<212> PRT
<213> Homo sapiens

<400> 543

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 544
<211> 32
<212> PRT
<213> Homo sapiens

<400> 544

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 545
<211> 74
<212> PRT
<213> Homo sapiens

<400> 545

Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro Ser Ala Cys
1 5 10 15

Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg Ile Met Asp
20 25 30

Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile Val Phe Ile
35 40 45

Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp Lys Trp Val
50 55 60

Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
65 70

<210> 546
<211> 32
<212> PRT
<213> Homo sapiens

<400> 546

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 547
<211> 32
<212> PRT
<213> Homo sapiens

<400> 547

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 548
<211> 32
<212> PRT
<213> Homo sapiens

<400> 548

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 549
<211> 32
<212> PRT
<213> Homo sapiens

<400> 549

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 550
<211> 32
<212> PRT

<213> Homo sapiens

<400> 550

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 551
<211> 32
<212> PRT
<213> Homo sapiens

<400> 551

Ser Ala Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 552
<211> 32
<212> PRT
<213> Homo sapiens

<400> 552

Ser Leu Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 553
<211> 32
<212> PRT
<213> Canis familiaris

<400> 553

Ser Pro Lys Met Met His Lys Ser Gly Cys Phe Gly Arg Arg Leu Asp
1 5 10 15

Arg Ile Gly Ser Leu Ser Gly Leu Gly Cys Asn Val Leu Arg Lys Tyr
20 25 30

<210> 554
<211> 32
<212> PRT
<213> Canis familiaris

<400> 554

Ser Pro Lys Met Met His Lys Ser Gly Cys Phe Gly Arg Arg Leu Asp
1 5 10 15

Arg Ile Gly Ser Leu Ser Gly Leu Gly Cys Asn Val Leu Arg Lys Tyr
20 25 30

<210> 555
<211> 32
<212> PRT
<213> Macaca fascicularis

<400> 555

Ser Pro Lys Met Val Arg Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 556
<211> 45
<212> PRT
<213> Rattus norvegicus

<400> 556

Ser Gln Asp Ser Ala Phe Arg Ile Gln Glu Arg Leu Arg Asn Ser Lys
1 5 10 15

Met Ala His Ser Ser Ser Cys Phe Gly Gln Lys Ile Asp Arg Ile Gly
20 25 30

Ala Val Ser Arg Leu Gly Cys Asp Gly Leu Arg Leu Phe
35 40 45

<210> 557
<211> 45
<212> PRT
<213> Rattus norvegicus

<400> 557

Ser Gln Asp Ser Ala Phe Arg Ile Gln Glu Arg Leu Arg Asn Ser Lys
1 5 10 15

Met Ala His Ser Ser Ser Cys Phe Gly Gln Lys Ile Asp Arg Ile Gly
20 25 30

Ala Val Ser Arg Leu Gly Cys Asp Gly Leu Arg Leu Phe
35 40 45

<210> 558

<211> 45
<212> PRT
<213> Mus musculus

<400> 558

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

Val Thr His Ile Ser Ser Cys Phe Gly His Lys Ile Asp Arg Ile Gly
20 25 30

Ser Val Ser Arg Leu Gly Cys Asn Ala Leu Lys Leu Leu
35 40 45

<210> 559
<211> 82
<212> PRT
<213> Homo sapiens

<400> 559

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro Gly Ile Gly Asp Pro Val Thr
35 40 45

Cys Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg
50 55 60

Tyr Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys
65 70 75 80

Lys Pro

<210> 560
<211> 32
<212> PRT
<213> Homo sapiens

<400> 560

Ser Pro Lys Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met Asp
1 5 10 15

Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg His
20 25 30

<210> 561
<211> 41
<212> PRT
<213> Homo sapiens

<400> 561

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro
35 40

<210> 562
<211> 41
<212> PRT
<213> Homo sapiens

<400> 562

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro
35 40

<210> 563
<211> 82
<212> PRT
<213> Homo sapiens

<400> 563

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro Gly Ile Gly Asp Pro Val Thr
35 40 45

Cys Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg
50 55 60

Tyr Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys

65 70 75 80

Lys Pro

<210> 564
<211> 82
<212> PRT
<213> Homo sapiens

<400> 564

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro Gly Ile Gly Asp Pro Val Thr
35 40 45

Cys Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg
50 55 60

Tyr Lys Gln Ile Gly Thr Cys Gly Leu Pro Gly Thr Lys Cys Cys Lys
65 70 75 80

Lys Pro

<210> 565
<211> 41
<212> PRT
<213> Homo sapiens

<400> 565

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro
35 40

<210> 566
<211> 41
<212> PRT
<213> Homo sapiens

<400> 566

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
20 25 30

Pro Gly Thr Lys Cys Cys Lys Lys Pro
35 40

<210> 567
<211> 82
<212> PRT
<213> Homo sapiens

<400> 567

Gly Ile Gly Asp Pro Val Thr Cys Leu Lys Ser Gly Ala Ile Cys His
1 5 10 15

Pro Val Phe Cys Pro Arg Arg Tyr Lys Gln Ile Gly Thr Cys Gly Leu
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Pro Gly Thr Lys Cys Cys Lys Lys Pro Gly Ile Gly Asp Pro Val Thr
35 40 45

Cys Leu Lys Ser Gly Ala Ile Cys His Pro Val Phe Cys Pro Arg Arg
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Lys Pro

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<400> 625
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gacttcgtgc aatggttgat gaacaccaag agaaacagaa ataacatc 108

<210> 626
<211> 1410
<212> DNA
<213> Influenza A virus

<400> 626
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agcttgatgt tacaaattgg gaacataatc tcaatatggg ttagtcattc aattcaaaca 120

gggaatcaac accaggctga accatgcaat caaagcatta ttacttatga aaacaacacc 180

tgggtaaacc agacatatgt caacatcagc aataccaatt ttcttactga gaaagctgtg 240

gcttcagtaa cattagcggg caattcatct ctttgcccca ttagtggatg ggctgtatac 300

agtaaggaca acggtataag aatcggttcc aaggggggatg tgtttgttat aagagagccg 360

ttcatctcat gctcccactt ggaatgcaga actttctttt tgactcaggg agccttgctg 420

aatgacaagc attctaatgg gaccgtcaaa gacagaagcc ctcacagaac attaatgagt 480

tgtcccgtgg gtgaggctcc ttccccatac aactcgaggt ttgagtctgt tgcttggtcg 540

gcaagtgctt gtcatgatgg cactagttgg ttgacaattg gaatttctgg cccagacaat 600

ggggctgtgg ctgtattgaa atacaatggc ataataacag acactatcaa gagttggagg 660

aacaacataa tgagaactca agagtctgaa tgtgcatgtg taaatggctc ttgctttact 720

gttatgactg atggaccaag taatgggcag gcttcataca aaatcttcag aatagaaaaa 780

gggaaagtag ttaaatcagc cgaattaaat gcccctaatt atcactatga ggagtgctcc 840

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cggccatggg tatctttcaa tcaaaatttg gagtatcgaa taggatatat atgcagtgga 960

gttttcggag acaatccacg ccccaatgat gggacaggca gttgtggtcc ggtgtcccct 1020

aaaggggcat atggaataaa agggttctca tttaaatacg gcaatggtgt ttggatcggg 1080

agaaccaaaa gcactaattc caggagcggc tttgaaatga tttgggatcc aaatggatgg 1140

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ggatatagcg ggagttttgt ccagcatcca gaactgacag gattagattg cataagacct 1260

tgtttctggg ttgagctaat cagagggcgg cccaaagaga gcacaatttg gactagtggg 1320

agcagcatat ccttttgtgg tgtaaatagt gacactgtgg gttggtcttg gccagacggt 1380

gctgagttgc cattcaccat tgacaagtag 1410

<210> 627
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<212> DNA
<213> Influenza A virus

<400> 627
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gggaatcaac accaggctga accatgcaat caaagcatta ttacttatga aaacaacacc 180

tgggtaaacc agacatatgt caacatcagc aataccaatt ttcttactga gaaagctgtg 240

gcttcagtaa cattagcggg caattcatct ctttgcccca ttagtggatg ggctgtatac 300

agtaaggaca acggtataag aatcggttcc aaggggggatg tgtttgttat aagagagccg 360

ttcatctcat gctcccactt ggaatgcaga actttctttt tgactcaggg agccttgctg 420

aatgacaagc attctaatgg gaccgtcaaa gacagaagcc ctcacagaac attaatgagt 480

tgtcccgtgg gtgaggctcc ttccccatac aactcgaggt ttgagtctgt tgcttggtcg 540

gcaagtgctt gtcatgatgg cactagttgg ttgacaattg gaatttctgg cccagacaat 600

ggggctgtgg ctgtattgaa atacaatggc ataataacag acactatcaa gagttggagg 660

aacaacataa tgagaactca agagtctgaa tgtgcatgtg taaatggctc ttgctttact 720

gttatgactg atggaccaag taatgggcag gcttcataca aaatcttcag aatagaaaaa 780

gggaaagtag ttaaatcagc cgaattaaat gcccctaatt atcactatga ggagtgctcc 840

tgttatcctg atgctggaga aatcacatgt gtgtgcaggg ataactggca tggctcaaat 900

cggccatggg tatctttcaa tcaaaatttg gagtatcgaa taggatatat atgcagtgga 960

gttttcggag acaatccacg ccccaatgat gggacaggca gttgtggtcc ggtgtcccct 1020

aaaggggcat atggaataaa agggttctca tttaaatacg gcaatggtgt ttggatcggg 1080

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tgtttctggg ttgagctaat cagagggcgg cccaaagaga gcacaatttg gactagtggg 1320

agcagcatat ccttttgtgg tgtaaatagt gacactgtgg gttggtcttg gccagacggt 1380

gctgagttgc cattcaccat tgacaagtag 1410

<210> 628
<211> 1708
<212> DNA
<213> Influenza A virus

<400> 628
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attggttacc atgcaaacaa ctcgacagag caggttgaca caataatgga aaagaacgtt 120

actgttacac atgcccaaga catactggaa aagacacaca acgggaagct ctgcgatcta 180

gatggagtga agcctctaat tttgagagat tgtagtgtag ctggatggct cctcggaaac 240

ccaatgtgtg acgaattcat caatgtgccg gaatggtctt acatagtgga gaaggccaat 300

ccagccaatg acctctgtta cccaggggat ttcaacgact atgaagaatt gaaacaccta 360

ttgagcagaa taaaccattt tgagaaaatt cagatcatcc ccaaaaattc ttggtccagt 420

catgaagcct cattaggggt gagctcagca tgtccatacc aaggaaagtc ctccttttc 480

aggaatgtgg tatggcttat caaaaagaac aatgcatacc caacaataaa gaggagctac 540

aataatacca accaagaaga tcttttggta ttgtgggggga ttcaccatcc taatgatgcg 600

gcagagcaga ctaggctcta tcaaaaccca accacctaca tttccgttgg gacatcaaca 660

ctaaaccaga gattggtacc aaaaatagct actagatcca aagtaaacgg gcaaaatgga 720

aggatggagt tcttctggac aattttaaaa ccgaatgatg caatcaactt cgagagcaat 780

ggaaatttca ttgctccaga atatgcatac aaaattgtca agaaagggga ctcagcaatt 840

atgaaaagtg aattggaata tggtaactgc aacaccaagt gtcaaactcc aatgggggcg 900

ataaactcta gtatgccatt ccacaatata caccctctca ccatcgggga atgccccaaa 960

tatgtgaaat caaacagatt agtccttgcg actgggctca gaaatagccc tcaaagagag 1020

agaagaagaa aaaagagagg attatttgga gctatagcag gttttataga gggaggatgg 1080

cagggaatgg tagatggttg gtatgggtac caccatagca atgagcaggg gagtgggtac 1140

gctgcagaca aagaatccac tcaaaaggca atagatggag tcaccaataa ggtcaactcg 1200

atcattgaca aaatgaacac tcagtttgag gccgttggaa gggaatttaa taacttagaa 1260

aggagaatag agaatttaaa caagaagatg gaagacggat tcctagatgt ctggacttat 1320

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ggaacgtatg actacccgca gtattcagaa gaagcaagac taaaaagaga ggaaataagt 1560

ggagtaaaat tggagtcaat aggaacttac caaatactgt caatttattc tacagtggcg 1620

agttccctag cactggcaat catggtagct ggtctatctt tatggatgtg ctccaatggg 1680

tcgttacaat gcagaatttg catttaag 1708

<210> 629
<211> 1708
<212> DNA

<213> Influenza A virus

<400> 629

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gatggagtga agcctctaat tttgagagat tgtagtgtag ctggatggct cctcggaaac 240

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ttgagcagaa taaaccattt tgagaaaatt cagatcatcc ccaaaaattc ttggtccagt 420

catgaagcct cattaggggt gagctcagca tgtccatacc aaggaaagtc ctccttttc 480

aggaatgtgg tatggcttat caaaaagaac aatgcatacc caacaataaa gaggagctac 540

aataatacca accaagaaga tcttttggta ttgtgggggа ttcaccatcc taatgatgcg 600

gcagagcaga ctaggctcta tcaaaaccca accacctaca tttccgttgg gacatcaaca 660

ctaaaccaga gattggtacc aaaaatagct actagatcca aagtaaacgg gcaaaatgga 720

aggatggagt tcttctggac aattttaaaa ccgaatgatg caatcaactt cgagagcaat 780

ggaaatttca ttgctccaga atatgcatac aaaattgtca agaaagggga ctcagcaatt 840

atgaaaagtg aattggaata tggtaactgc aacaccaagt gtcaaactcc aatgggggcg 900

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tatgtgaaat caaacagatt agtccttgcg actgggctca gaaatagccc tcaaagagag 1020

agaagaagaa aaaagagagg attatttgga gctatagcag gttttataga gggaggatgg 1080

cagggaatgg tagatggttg gtatgggtac caccatagca atgagcaggg gagtgggtac 1140

gctgcagaca aagaatccac tcaaaaggca atagatggag tcaccaataa ggtcaactcg 1200

atcattgaca aaatgaacac tcagtttgag gccgttggaa gggaatttaa taacttagaa 1260

aggagaatag agaatttaaa caagaagatg gaagacggat tcctagatgt ctggacttat 1320

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tcgttacaat gcagaatttg catttaag 1708

<210> 630

<211> 1809
<212> DNA
<213> Homo sapiens

<400> 630
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atgcttattg ggaagtcaca tactgaagat gacatcataa ttgcaacaaa gaatggaaaa 120

gtcagaggga tgaacttgac agtttttggt ggcacggtaa cagcctttct tggaattccc 180

tatgcacagc cacctcttgg tagacttcga ttcaaaaagc cacagtctct gaccaagtgg 240

tctgatattt ggaatgccac aaaatatgca aattcttgct gtcagaacat agatcaaagt 300

tttccaggct tccatggatc agagatgtgg aacccaaaca ctgacctcag tgaagactgt 360

ttatatctaa atgtatggat tccagcacct aaaccaaaaa atgccactgt attgatatgg 420

atttatggtg gtggttttca aactggaaca tcatctttac atgtttatga tggcaagttt 480

ctggctcggg ttgaaagagt tattgtagtg tcaatgaact atagggtggg tgccctagga 540

ttcttagctt tgccaggaaa tcctgaggct ccagggaaca tgggtttatt tgatcaacag 600

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agccattcat tgttcaccag agccattctg caaagtggat cctttaatgc tccttgggcg 780

gtaacatctc tttatgaagc taggaacaga acgttgaact tagctaaatt gactggttgc 840

tctagagaga atgagactga aataatcaag tgtcttagaa ataaagatcc ccaagaaatt 900

cttctgaatg aagcatttgt tgtcccctat gggactcctt tgtcagtaaa ctttggtccg 960

accgtggatg gtgattttct cactgacatg ccagacatat tacttgaact tggacaattt 1020

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aattttgcaa aatatgggaa tccaaatgag actcagaaca atagcacaag ctggcctgtc 1560

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aaactacgtg ctcaacaatg tcgattctgg acatcatttt ttccaaaagt cttggaaatg 1680

acaggaaata ttgatgaagc agaatgggag tggaaagcag gattccatcg ctggaacaat 1740

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ggtctctaa 1809

<210> 631
<211> 1809
<212> DNA
<213> Homo sapiens

<400> 631
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atgcttattg ggaagtcaca tactgaagat gacatcataa ttgcaacaaa gaatggaaaa 120

gtcagaggga tgaacttgac agtttttggt ggcacggtaa cagcctttct tggaattccc 180

tatgcacagc cacctcttgg tagacttcga ttcaaaaagc cacagtctct gaccaagtgg 240

tctgatattt ggaatgccac aaaatatgca aattcttgct gtcagaacat agatcaaagt 300

tttccaggct tccatggatc agagatgtgg aacccaaaca ctgacctcag tgaagactgt 360

ttatatctaa atgtatggat tccagcacct aaaccaaaaa atgccactgt attgatatgg 420

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ctggctcggg ttgaaagagt tattgtagtg tcaatgaact atagggtggg tgccctagga 540

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agccattcat tgttcaccag agccattctg caaagtggat cctttaatgc tccttgggcg 780

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tctagagaga atgagactga aataatcaag tgtcttagaa ataaagatcc ccaagaaatt 900

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accgtggatg gtgattttct cactgacatg ccagacatat tacttgaact tggacaattt 1020

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agagataatt acacaaaagc cgaggaaatt ttgagtagat ccatagtgaa acggtgggca 1500

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ttcaaaagca ctgaacaaaa atatctaacc ttgaatacag agtcaacaag aataatgacg 1620

aaactacgtg ctcaacaatg tcgattctgg acatcatttt ttccaaaagt cttggaaatg 1680

acaggaaata ttgatgaagc agaatgggag tggaaagcag gattccatcg ctggaacaat 1740

tacatgatgg actggaaaaa tcaatttaac gattacacta gcaagaaaga aagttgtgtg 1800

ggtctctaa 1809

<210> 632
<211> 156
<212> DNA
<213> Homo sapiens

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gttgctccaa gatctaagat ttctccacaa ggttac 156

<210> 633
<211> 156
<212> DNA
<213> Homo sapiens

<400> 633
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gttgctccaa gatctaagat ttctccacaa ggttac 156

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<211> 108
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tacgcctccc tgcgccacta cctcaacctg gtcacccggc agcggtat 108

<210> 635
<211> 108
<212> DNA
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<210> 636
<211> 501
<212> DNA
<213> Homo sapiens

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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

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<210> 637
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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

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<210> 638
<211> 501
<212> DNA
<213> Homo sapiens

<400> 638
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gaggagtttg gcaaccagtt ccaaaaggct gaaaccatcc ctgtcctcca tgagatgatc 180

cagcagatct tcaatctctt cagcacaaag gactcatctg ctgcttggga tgagaccctc 240

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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

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gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

ttaagaagta aggaataata a 501

<210> 639
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<213> Homo sapiens

<400> 639
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ttaagaagta aggaataata a 501

<210> 640
<211> 501
<212> DNA
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<400> 640
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caggggtgg gggtgacaga gactcccctg atgaaggagg actccattct ggctgtgagg 360

aaatacttcc aaagaatcac tctctatctg aaagagaaga aatacagccc ttgtgcctgg 420

gaggttgtca gagcagaaat catgagatct ttttctttgt caacaaactt gcaagaaagt 480

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<210> 641
<211> 685
<212> PRT
<213> Homo sapiens

<400> 641

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1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser

```
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495
```

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Gln His His Gly Val Thr Lys Cys Asn Ile Thr Cys Ser Lys Met
610 615 620

Thr Ser Lys Ile Pro Val Ala Leu Leu Ile His Tyr Gln Gln Asn Gln
625 630 635 640

Ala Ser Cys Gly Lys Arg Ala Ile Ile Leu Glu Thr Arg Gln His Arg
645 650 655

Leu Phe Cys Ala Asp Pro Lys Glu Gln Trp Val Lys Asp Ala Met Gln
660 665 670

His Leu Asp Arg Gln Ala Ala Ala Leu Thr Arg Asn Gly
675 680 685

<210> 642
<211> 685
<212> PRT
<213> Homo sapiens

<400> 642

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gln His His Gly Val Thr Lys Cys
20 25 30

```
Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
        35                  40                  45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
    50                  55                  60

Leu Glu Thr Arg Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln
65                  70                  75                  80

Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
                85                  90                  95

Thr Arg Asn Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
            100                 105                 110

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
        115                 120                 125

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
    130                 135                 140

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
145                 150                 155                 160

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
                165                 170                 175

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
            180                 185                 190

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
        195                 200                 205

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
    210                 215                 220

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
225                 230                 235                 240

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
                245                 250                 255

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
            260                 265                 270

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
        275                 280                 285
```

```
Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
    290                 295                 300

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
305                 310                 315                 320

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
                325                 330                 335

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
            340                 345                 350

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
        355                 360                 365

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
    370                 375                 380

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
385                 390                 395                 400

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
                405                 410                 415

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
            420                 425                 430

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
        435                 440                 445

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
    450                 455                 460

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
465                 470                 475                 480

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
                485                 490                 495

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
            500                 505                 510

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
        515                 520                 525

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
    530                 535                 540
```

```
Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
545                 550                 555                 560

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
                565                 570                 575

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
            580                 585                 590

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
        595                 600                 605

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
    610                 615                 620

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
625                 630                 635                 640

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
                645                 650                 655

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
            660                 665                 670

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        675                 680                 685


<210>  643
<211>  685
<212>  PRT
<213>  Homo sapiens

<400>  643

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Gln His His Gly Val Thr Lys Cys
            20                  25                  30

Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
        35                  40                  45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
    50                  55                  60

Leu Glu Thr Arg Gln His Gln Leu Phe Cys Ala Asp Pro Lys Glu Gln
65                  70                  75                  80
```

```
Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
                85                  90                  95

Thr Arg Asn Gly Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
            100                 105                 110

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala
        115                 120                 125

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
    130                 135                 140

Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
145                 150                 155                 160

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
                165                 170                 175

Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala
            180                 185                 190

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
        195                 200                 205

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
    210                 215                 220

Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr
225                 230                 235                 240

Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
                245                 250                 255

Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
            260                 265                 270

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
        275                 280                 285

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
    290                 295                 300

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
305                 310                 315                 320

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
```

325 330 335

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
340 345 350

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
355 360 365

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
370 375 380

Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala
385 390 395 400

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys
405 410 415

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
420 425 430

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
435 440 445

Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
450 455 460

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
465 470 475 480

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
485 490 495

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
500 505 510

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
515 520 525

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
530 535 540

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
545 550 555 560

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
565 570 575

```
Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
            580                 585                 590

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
        595                 600                 605

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
    610                 615                 620

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
625                 630                 635                 640

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
                645                 650                 655

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
            660                 665                 670

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        675                 680                 685


<210>  644
<211>  681
<212>  PRT
<213>  Homo sapiens

<400>  644

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Thr Lys Cys Asn Ile Thr Cys
            20                  25                  30

Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu Ile His Tyr Gln
        35                  40                  45

Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile Leu Glu Thr Arg
    50                  55                  60

Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln Trp Val Lys Asp
65                  70                  75                  80

Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu Thr Arg Asn Gly
                85                  90                  95

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
            100                 105                 110
```

```
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
        115                 120                 125

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
    130                 135                 140

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
145                 150                 155                 160

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
                165                 170                 175

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
            180                 185                 190

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
        195                 200                 205

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
    210                 215                 220

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
225                 230                 235                 240

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
                245                 250                 255

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
            260                 265                 270

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
        275                 280                 285

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
    290                 295                 300

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
305                 310                 315                 320

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
                325                 330                 335

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
            340                 345                 350

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
        355                 360                 365
```

```
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
    370                 375                 380

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
385                 390                 395                 400

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
                405                 410                 415

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
            420                 425                 430

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
        435                 440                 445

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
    450                 455                 460

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
465                 470                 475                 480

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
                485                 490                 495

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
            500                 505                 510

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
        515                 520                 525

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
    530                 535                 540

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
545                 550                 555                 560

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
                565                 570                 575

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
            580                 585                 590

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
        595                 600                 605

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
    610                 615                 620
```

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
625 630 635 640

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
645 650 655

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
660 665 670

Ala Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 645
<211> 641
<212> PRT
<213> Homo sapiens

<400> 645

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr
20 25 30

Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr
35 40 45

Lys Arg Asn Arg Asn Asn Ile Ala Asp Ala His Lys Ser Glu Val Ala
50 55 60

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
65 70 75 80

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
85 90 95

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
100 105 110

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
115 120 125

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
130 135 140

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
145 150 155 160

```
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
                165                 170                 175

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
            180                 185                 190

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
        195                 200                 205

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
    210                 215                 220

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
225                 230                 235                 240

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
                245                 250                 255

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
            260                 265                 270

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
        275                 280                 285

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
    290                 295                 300

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
305                 310                 315                 320

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
                325                 330                 335

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
            340                 345                 350

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
        355                 360                 365

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
    370                 375                 380

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
385                 390                 395                 400

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
```

405 410 415

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
420 425 430

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
435 440 445

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
450 455 460

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
465 470 475 480

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
485 490 495

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
500 505 510

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
515 520 525

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
530 535 540

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
545 550 555 560

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
565 570 575

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
580 585 590

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
595 600 605

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
610 615 620

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
625 630 635 640

Leu

<210> 646
<211> 691
<212> PRT
<213> Homo sapiens

<400> 646

Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1 5 10 15

Ile Ser Ala Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
20 25 30

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
35 40 45

Thr Arg Gln Arg Tyr Asp Ala His Lys Ser Glu Val Ala His Arg Phe
50 55 60

Lys Asp Leu Gly Glu Asp Ala His Lys Ser Glu Val Ala His Arg Phe
65 70 75 80

Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe
85 90 95

Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val
100 105 110

Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
115 120 125

Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
130 135 140

Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys
145 150 155 160

Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
165 170 175

Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met
180 185 190

Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu
195 200 205

Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
210 215 220

```
Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala
225                 230                 235                 240

Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp
                245                 250                 255

Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu
            260                 265                 270

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu
        275                 280                 285

Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val
    290                 295                 300

Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu
305                 310                 315                 320

Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn
                325                 330                 335

Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu
            340                 345                 350

Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro
        355                 360                 365

Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val
    370                 375                 380

Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu
385                 390                 395                 400

Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu
                405                 410                 415

Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala
            420                 425                 430

Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro
        435                 440                 445

Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe
    450                 455                 460

Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr
465                 470                 475                 480
```

```
Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser
                485                 490                 495

Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala
            500                 505                 510

Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln
        515                 520                 525

Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys
    530                 535                 540

Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu
545                 550                 555                 560

Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe
                565                 570                 575

Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile
            580                 585                 590

Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala
        595                 600                 605

Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val
    610                 615                 620

Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu
625                 630                 635                 640

Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu His Ser
                645                 650                 655

Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg
            660                 665                 670

Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn Arg Asn
        675                 680                 685

Asn Ile Ala
    690
```

<210> 647
<211> 646
<212> PRT
<213> Homo sapiens

<400> 647

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255
```

```
Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
```

```
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp
    610                 615                 620

Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg
625                 630                 635                 640

Asn Arg Asn Asn Ile Ala
                645
```

<210> 648
<211> 630
<212> PRT
<213> Artificial sequence

<220>
<223> Invertase signal sequence followed by killer toxin peptide fused via a 16 amino acid linker from HSA (amino acids 25-40) to mature HSA.

<400> 648

```
Met Leu Leu Gln Ala Phe Leu Phe Leu Leu Ala Gly Phe Ala Ala Lys
1               5                   10                  15

Ile Ser Ala Ala Lys Val Thr Met Thr Cys Ser Ala Ser Asp Ala His
            20                  25                  30

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Asp Ala His
        35                  40                  45
```

```
Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
    50                  55                  60

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
65                  70                  75                  80

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
                85                  90                  95

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
            100                 105                 110

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
        115                 120                 125

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
    130                 135                 140

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
145                 150                 155                 160

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
                165                 170                 175

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
            180                 185                 190

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
        195                 200                 205

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
    210                 215                 220

Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
225                 230                 235                 240

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
                245                 250                 255

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
            260                 265                 270

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
        275                 280                 285

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
    290                 295                 300
```

```
Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
305                 310                 315                 320

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
                325                 330                 335

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
            340                 345                 350

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
        355                 360                 365

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
    370                 375                 380

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
385                 390                 395                 400

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
                405                 410                 415

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
            420                 425                 430

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
        435                 440                 445

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
    450                 455                 460

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
465                 470                 475                 480

Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
                485                 490                 495

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
            500                 505                 510

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
        515                 520                 525

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
    530                 535                 540

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
545                 550                 555                 560
```

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
565 570 575

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
580 585 590

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
595 600 605

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
610 615 620

Gln Ala Ala Leu Gly Leu
625 630

<210> 649
<211> 646
<212> PRT
<213> Homo sapiens

<400> 649

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

```
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
```

385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp
610 615 620

Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg
625 630 635 640

Asn Arg Asn Asn Ile Ala
645

<210> 650
<211> 737
<212> PRT
<213> Homo sapiens

<400> 650

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Cys Ser Cys Ala Pro Ala His Pro
20 25 30

Gln Gln His Ile Cys His Ser Ala Leu Val Ile Arg Ala Lys Ile Ser
35 40 45

Ser Glu Lys Val Val Pro Ala Ser Ala Asp Pro Ala Asp Thr Glu Lys
50 55 60

Met Leu Arg Tyr Glu Ile Lys Gln Ile Lys Met Phe Lys Gly Phe Glu
65 70 75 80

Lys Val Lys Asp Val Gln Tyr Ile Tyr Thr Pro Phe Asp Ser Ser Leu
85 90 95

Cys Gly Val Lys Leu Glu Ala Asn Ser Gln Lys Gln Tyr Leu Leu Thr
100 105 110

Gly Gln Val Leu Ser Asp Gly Lys Val Phe Ile His Leu Cys Asn Tyr
115 120 125

Ile Glu Pro Trp Glu Asp Leu Ser Leu Val Gln Arg Glu Ser Leu Asn
130 135 140

His His Tyr His Leu Asn Cys Gly Asp Ala His Lys Ser Glu Val Ala
145 150 155 160

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
165 170 175

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
180 185 190

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
195 200 205

```
Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
    210                 215                 220

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
225                 230                 235                 240

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
                245                 250                 255

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
            260                 265                 270

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
        275                 280                 285

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
    290                 295                 300

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
305                 310                 315                 320

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
                325                 330                 335

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
            340                 345                 350

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
        355                 360                 365

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
    370                 375                 380

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
385                 390                 395                 400

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
                405                 410                 415

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
            420                 425                 430

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
        435                 440                 445

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
    450                 455                 460
```

```
Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
465                 470                 475                 480

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
                485                 490                 495

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
            500                 505                 510

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
        515                 520                 525

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
    530                 535                 540

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
545                 550                 555                 560

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
                565                 570                 575

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
            580                 585                 590

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
        595                 600                 605

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
    610                 615                 620

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
625                 630                 635                 640

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
                645                 650                 655

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
            660                 665                 670

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
        675                 680                 685

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
    690                 695                 700

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
705                 710                 715                 720
```

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
725 730 735

Leu

<210> 651
<211> 737
<212> PRT
<213> Homo sapiens

<400> 651

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

```
Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
```

```
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Ser Cys Ala Pro Ala His Pro Gln Gln His Ile Cys His Ser
    610                 615                 620

Ala Leu Val Ile Arg Ala Lys Ile Ser Ser Glu Lys Val Val Pro Ala
625                 630                 635                 640

Ser Ala Asp Pro Ala Asp Thr Glu Lys Met Leu Arg Tyr Glu Ile Lys
                645                 650                 655

Gln Ile Lys Met Phe Lys Gly Phe Glu Lys Val Lys Asp Val Gln Tyr
            660                 665                 670

Ile Tyr Thr Pro Phe Asp Ser Ser Leu Cys Gly Val Lys Leu Glu Ala
        675                 680                 685
```

Asn Ser Gln Lys Gln Tyr Leu Leu Thr Gly Gln Val Leu Ser Asp Gly
690 695 700

Lys Val Phe Ile His Leu Cys Asn Tyr Ile Glu Pro Trp Glu Asp Leu
705 710 715 720

Ser Leu Val Gln Arg Glu Ser Leu Asn His His Tyr His Leu Asn Cys
725 730 735

Gly

<210> 652
<211> 677
<212> PRT
<213> Homo sapiens

<400> 652

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

```
Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415
```

```
Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
    610                 615                 620

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625                 630                 635                 640

Gln Arg Tyr Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
                645                 650                 655

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
            660                 665                 670
```

Thr Arg Gln Arg Tyr
675

<210> 653
<211> 642
<212> PRT
<213> Homo sapiens

<400> 653

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly Ile Lys Pro Glu Ala Pro Gly Glu Asp
20 25 30

Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr
35 40 45

Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys Ser Glu Val
50 55 60

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
65 70 75 80

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
85 90 95

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
100 105 110

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
115 120 125

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
130 135 140

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
145 150 155 160

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
165 170 175

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
180 185 190

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
195 200 205

```
Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
    210                 215                 220

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
225                 230                 235                 240

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
                245                 250                 255

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
            260                 265                 270

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
        275                 280                 285

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
    290                 295                 300

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
305                 310                 315                 320

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
                325                 330                 335

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
            340                 345                 350

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
        355                 360                 365

Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
    370                 375                 380

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
385                 390                 395                 400

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
                405                 410                 415

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
            420                 425                 430

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
        435                 440                 445

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
```

```
    450                 455                 460

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
465                 470                 475                 480

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
                485                 490                 495

His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val
            500                 505                 510

Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp
        515                 520                 525

Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys
    530                 535                 540

Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn
545                 550                 555                 560

Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys
                565                 570                 575

Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His
            580                 585                 590

Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe
        595                 600                 605

Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
    610                 615                 620

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
625                 630                 635                 640

Gly Leu
```

<210> 654
<211> 661
<212> PRT
<213> Homo sapiens

<400> 654

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Gly Ser Leu Asp Lys Arg Tyr Arg Gln Ser Met Asn Asn Phe
```

```
            20                  25                  30

Gln Gly Leu Arg Ser Phe Gly Cys Arg Phe Gly Thr Cys Thr Val Gln
        35                  40                  45

Lys Leu Ala His Gln Ile Tyr Gln Phe Thr Asp Lys Asp Lys Asp Asn
    50                  55                  60

Val Ala Pro Arg Ser Lys Ile Ser Pro Gln Gly Tyr Asp Ala His Lys
65                  70                  75                  80

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
                85                  90                  95

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
            100                 105                 110

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
        115                 120                 125

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
    130                 135                 140

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
145                 150                 155                 160

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
                165                 170                 175

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
            180                 185                 190

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
        195                 200                 205

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
    210                 215                 220

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
225                 230                 235                 240

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
                245                 250                 255

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
            260                 265                 270
```

```
Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
        275                 280                 285

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
    290                 295                 300

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
305                 310                 315                 320

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
                325                 330                 335

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
            340                 345                 350

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
        355                 360                 365

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
    370                 375                 380

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
385                 390                 395                 400

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
                405                 410                 415

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
            420                 425                 430

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
        435                 440                 445

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
    450                 455                 460

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
465                 470                 475                 480

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
                485                 490                 495

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
            500                 505                 510

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
        515                 520                 525
```

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
530 535 540

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
545 550 555 560

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
565 570 575

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
580 585 590

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
595 600 605

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
610 615 620

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
625 630 635 640

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
645 650 655

Ala Ala Leu Gly Leu
660

<210> 655
<211> 645
<212> PRT
<213> Homo sapiens

<400> 655

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly His Ser Gln Gly Thr Phe Thr Ser Asp
20 25 30

Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp
35 40 45

Leu Met Asn Thr Lys Arg Asn Arg Asn Asn Ile Ala Asp Ala His Lys
50 55 60

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
65 70 75 80

```
Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
                85                  90                  95

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
            100                 105                 110

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
        115                 120                 125

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
    130                 135                 140

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
145                 150                 155                 160

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
                165                 170                 175

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
            180                 185                 190

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
        195                 200                 205

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
    210                 215                 220

Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
225                 230                 235                 240

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
                245                 250                 255

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
            260                 265                 270

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
        275                 280                 285

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
    290                 295                 300

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
305                 310                 315                 320

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
                325                 330                 335
```

```
Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
            340                 345                 350

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
        355                 360                 365

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
    370                 375                 380

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
385                 390                 395                 400

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
                405                 410                 415

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
            420                 425                 430

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
        435                 440                 445

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
    450                 455                 460

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
465                 470                 475                 480

Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
                485                 490                 495

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
            500                 505                 510

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
        515                 520                 525

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
    530                 535                 540

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
545                 550                 555                 560

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
                565                 570                 575

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
```

580 585 590

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
595 600 605

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
610 615 620

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
625 630 635 640

Ala Ala Leu Gly Leu
645

<210> 656
<211> 637
<212> PRT
<213> Homo sapiens

<400> 656

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys

```
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400
```

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Gly Ser Ser Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg
610 615 620

Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro Arg
625 630 635

<210> 657
<211> 637
<212> PRT

<213> Homo sapiens

<400> 657

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240
```

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Gly Ser Ser Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg
610 615 620

Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro Arg
625 630 635

<210> 658
<211> 639
<212> PRT
<213> Homo sapiens

<400> 658

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Val Thr His Arg Leu Ala Gly Leu
20 25 30

Leu Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn
35 40 45

Val Gly Ser Lys Ala Phe Asp Ala His Lys Ser Glu Val Ala His Arg
50 55 60

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
65 70 75 80

```
Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
                85                  90                  95

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
            100                 105                 110

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
        115                 120                 125

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
    130                 135                 140

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
145                 150                 155                 160

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
                165                 170                 175

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
            180                 185                 190

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
        195                 200                 205

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
    210                 215                 220

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
225                 230                 235                 240

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
                245                 250                 255

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
            260                 265                 270

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
        275                 280                 285

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
    290                 295                 300

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
305                 310                 315                 320

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
```

```
                325                 330                 335

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
            340                 345                 350

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
        355                 360                 365

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
    370                 375                 380

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
385                 390                 395                 400

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
                405                 410                 415

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
            420                 425                 430

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        435                 440                 445

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    450                 455                 460

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
465                 470                 475                 480

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                485                 490                 495

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            500                 505                 510

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        515                 520                 525

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    530                 535                 540

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
545                 550                 555                 560

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                565                 570                 575
```

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
580 585 590

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
595 600 605

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
610 615 620

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 659
<211> 639
<212> PRT
<213> Homo sapiens

<400> 659

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

```
Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Val Thr His Arg Leu Ala Gly Leu Leu Ser Arg Ser Gly Gly Val
    610                 615                 620

Val Lys Asn Asn Phe Val Pro Thr Asn Val Gly Ser Lys Ala Phe
625                 630                 635
```

<210> 660
<211> 635
<212> PRT
<213> Homo sapiens

<400> 660

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Leu Ala Gly Leu Leu Ser Arg Ser
            20                  25                  30

Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val Gly Ser Lys
        35                  40                  45

Ala Phe Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
    50                  55                  60

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
65                  70                  75                  80

Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
                85                  90                  95

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
            100                 105                 110

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
        115                 120                 125

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
    130                 135                 140

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
145                 150                 155                 160

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
                165                 170                 175

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
            180                 185                 190

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
        195                 200                 205

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
    210                 215                 220

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
225                 230                 235                 240

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
                245                 250                 255
```

```
Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
            260                 265                 270

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
        275                 280                 285

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
    290                 295                 300

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
305                 310                 315                 320

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
                325                 330                 335

Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
            340                 345                 350

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
        355                 360                 365

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
    370                 375                 380

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
385                 390                 395                 400

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
                405                 410                 415

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
            420                 425                 430

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
        435                 440                 445

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
    450                 455                 460

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
465                 470                 475                 480

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
                485                 490                 495

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
```

```
            500                 505                 510

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
        515                 520                 525

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
    530                 535                 540

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
545                 550                 555                 560

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
                565                 570                 575

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
            580                 585                 590

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
        595                 600                 605

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
    610                 615                 620

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625                 630                 635


<210>  661
<211>  635
<212>  PRT
<213>  Homo sapiens

<400>  661

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
```

```
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335
```

```
Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590
```

```
Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Leu Ala Gly Leu Leu Ser Arg Ser Gly Gly Val Val Lys Asn Asn
    610                 615                 620

Phe Val Pro Thr Asn Val Gly Ser Lys Ala Phe
625                 630                 635


<210>  662
<211>  714
<212>  PRT
<213>  Homo sapiens

<400>  662

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175
```

```
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430
```

```
Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln
    610                 615                 620

Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr
625                 630                 635                 640

Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys
                645                 650                 655

Cys Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro
            660                 665                 670

Leu Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr
```

675 680 685

Asp Met Pro Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg
690 695 700

Gly Ser Ala Gly Asn Lys Asn Tyr Arg Met
705 710

<210> 663
<211> 714
<212> PRT
<213> Homo sapiens

<400> 663

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Gly Pro Glu Thr Leu Cys Gly Ala
20 25 30

Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr
35 40 45

Phe Asn Lys Pro Thr Gly Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln
50 55 60

Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp Leu Arg Arg
65 70 75 80

Leu Glu Met Tyr Cys Ala Pro Leu Lys Pro Ala Lys Ser Ala Arg Ser
85 90 95

Val Arg Ala Gln Arg His Thr Asp Met Pro Lys Thr Gln Lys Glu Val
100 105 110

His Leu Lys Asn Ala Ser Arg Gly Ser Ala Gly Asn Lys Asn Tyr Arg
115 120 125

Met Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
130 135 140

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
145 150 155 160

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
165 170 175

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp

```
            180                 185                 190

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
        195                 200                 205

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
    210                 215                 220

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
225                 230                 235                 240

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
                245                 250                 255

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
            260                 265                 270

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
        275                 280                 285

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
    290                 295                 300

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
305                 310                 315                 320

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
                325                 330                 335

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
            340                 345                 350

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
        355                 360                 365

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
    370                 375                 380

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
385                 390                 395                 400

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
                405                 410                 415

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
            420                 425                 430
```

```
Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
        435                 440                 445

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
    450                 455                 460

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
465                 470                 475                 480

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
                485                 490                 495

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
            500                 505                 510

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
        515                 520                 525

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
    530                 535                 540

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
545                 550                 555                 560

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
                565                 570                 575

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
            580                 585                 590

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
        595                 600                 605

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
    610                 615                 620

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
625                 630                 635                 640

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
                645                 650                 655

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
            660                 665                 670

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
        675                 680                 685
```

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
690 695 700

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
705 710

<210> 664
<211> 682
<212> PRT
<213> Homo sapiens

<400> 664

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly His Ser Gln Gly Thr Phe Thr Ser Asp
20 25 30

Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp
35 40 45

Leu Met Asn Thr Lys Arg Asn Arg Asn Asn Ile Ala His Ser Gln Gly
50 55 60

Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln
65 70 75 80

Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn Arg Asn Asn Ile
85 90 95

Ala Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly
100 105 110

Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu
115 120 125

Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr
130 135 140

Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp
145 150 155 160

Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr
165 170 175

Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu
180 185 190

```
Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn
        195                 200                 205

Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe
    210                 215                 220

His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala
225                 230                 235                 240

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys
                245                 250                 255

Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala
            260                 265                 270

Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala
        275                 280                 285

Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly
    290                 295                 300

Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe
305                 310                 315                 320

Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr
                325                 330                 335

Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp
            340                 345                 350

Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile
        355                 360                 365

Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser
    370                 375                 380

His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro
385                 390                 395                 400

Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr
                405                 410                 415

Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala
            420                 425                 430

Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys
        435                 440                 445
```

Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His
450 455 460

Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu
465 470 475 480

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
485 490 495

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
500 505 510

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
515 520 525

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
530 535 540

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
545 550 555 560

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
565 570 575

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
580 585 590

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
595 600 605

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
610 615 620

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
625 630 635 640

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
645 650 655

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
660 665 670

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
675 680

<210> 665

<211> 1056
<212> PRT
<213> Artificial sequence

<220>
<223> HSA/Kex-2 signal sequence followed an N-terminally truncated form of neuraminidase from Influenza A/Hong Kong/213/03 (HK213;H5N1) (amino acids 35-469) fused via a Gly-Ser linker (GGGGSGGGGSGG) to the N-terminus of mature HSA.

<400> 665

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15


Tyr Ser Arg Ser Leu Asp Lys Arg Ser His Ser Ile Gln Thr Gly Asn
            20                  25                  30


Gln His Gln Ala Glu Pro Cys Asn Gln Ser Ile Ile Thr Tyr Glu Asn
        35                  40                  45


Asn Thr Trp Val Asn Gln Thr Tyr Val Asn Ile Ser Asn Thr Asn Phe
    50                  55                  60


Leu Thr Glu Lys Ala Val Ala Ser Val Thr Leu Ala Gly Asn Ser Ser
65                  70                  75                  80


Leu Cys Pro Ile Ser Gly Trp Ala Val Tyr Ser Lys Asp Asn Gly Ile
                85                  90                  95


Arg Ile Gly Ser Lys Gly Asp Val Phe Val Ile Arg Glu Pro Phe Ile
            100                 105                 110


Ser Cys Ser His Leu Glu Cys Arg Thr Phe Phe Leu Thr Gln Gly Ala
        115                 120                 125


Leu Leu Asn Asp Lys His Ser Asn Gly Thr Val Lys Asp Arg Ser Pro
    130                 135                 140


His Arg Thr Leu Met Ser Cys Pro Val Gly Glu Ala Pro Ser Pro Tyr
145                 150                 155                 160


Asn Ser Arg Phe Glu Ser Val Ala Trp Ser Ala Ser Ala Cys His Asp
                165                 170                 175


Gly Thr Ser Trp Leu Thr Ile Gly Ile Ser Gly Pro Asp Asn Gly Ala
            180                 185                 190


Val Ala Val Leu Lys Tyr Asn Gly Ile Ile Thr Asp Thr Ile Lys Ser
        195                 200                 205
```

```
Trp Arg Asn Asn Ile Met Arg Thr Gln Glu Ser Glu Cys Ala Cys Val
    210                 215                 220

Asn Gly Ser Cys Phe Thr Val Met Thr Asp Gly Pro Ser Asn Gly Gln
225                 230                 235                 240

Ala Ser Tyr Lys Ile Phe Arg Ile Glu Lys Gly Lys Val Val Lys Ser
                245                 250                 255

Ala Glu Leu Asn Ala Pro Asn Tyr His Tyr Glu Glu Cys Ser Cys Tyr
            260                 265                 270

Pro Asp Ala Gly Glu Ile Thr Cys Val Cys Arg Asp Asn Trp His Gly
        275                 280                 285

Ser Asn Arg Pro Trp Val Ser Phe Asn Gln Asn Leu Glu Tyr Arg Ile
    290                 295                 300

Gly Tyr Ile Cys Ser Gly Val Phe Gly Asp Asn Pro Arg Pro Asn Asp
305                 310                 315                 320

Gly Thr Gly Ser Cys Gly Pro Val Ser Pro Lys Gly Ala Tyr Gly Ile
                325                 330                 335

Lys Gly Phe Ser Phe Lys Tyr Gly Asn Gly Val Trp Ile Gly Arg Thr
            340                 345                 350

Lys Ser Thr Asn Ser Arg Ser Gly Phe Glu Met Ile Trp Asp Pro Asn
        355                 360                 365

Gly Trp Thr Gly Thr Asp Ser Asn Phe Ser Val Lys Gln Asp Ile Val
    370                 375                 380

Ala Ile Thr Asp Trp Ser Gly Tyr Ser Gly Ser Phe Val Gln His Pro
385                 390                 395                 400

Glu Leu Thr Gly Leu Asp Cys Ile Arg Pro Cys Phe Trp Val Glu Leu
                405                 410                 415

Ile Arg Gly Arg Pro Lys Glu Ser Thr Ile Trp Thr Ser Gly Ser Ser
            420                 425                 430

Ile Ser Phe Cys Gly Val Asn Ser Asp Thr Val Gly Trp Ser Trp Pro
        435                 440                 445

Asp Gly Ala Glu Leu Pro Phe Thr Ile Asp Lys Gly Gly Gly Gly Ser
    450                 455                 460
```

```
Gly Gly Gly Gly Ser Gly Gly Asp Ala His Lys Ser Glu Val Ala His
465                 470                 475                 480

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
                485                 490                 495

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
            500                 505                 510

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
        515                 520                 525

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
    530                 535                 540

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
545                 550                 555                 560

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
                565                 570                 575

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
            580                 585                 590

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
        595                 600                 605

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
    610                 615                 620

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
625                 630                 635                 640

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu
                645                 650                 655

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
            660                 665                 670

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
        675                 680                 685

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
    690                 695                 700

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
```

705 710 715 720

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
725 730 735

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
740 745 750

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
755 760 765

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
770 775 780

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
785 790 795 800

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
805 810 815

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
820 825 830

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
835 840 845

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
850 855 860

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
865 870 875 880

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
885 890 895

Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
900 905 910

Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu
915 920 925

Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val
930 935 940

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
945 950 955 960

Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu
965 970 975

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg
980 985 990

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro
995 1000 1005

Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
1010 1015 1020

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys
1025 1030 1035

Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
1040 1045 1050

Leu Gly Leu
1055

<210> 666
<211> 1055
<212> PRT
<213> Artificial sequence

<220>
<223> A consensus signal sequence followed by an N-terminally truncated form of neuraminidase from Influenza A/Hong Kong/213/03 (HK213;H5N1)(amino acids 35-469) fused via a Gly-Ser linker (GGGGSGGGGSGG) to the N-terminus of mature HSA.

<400> 666

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly Ser His Ser Ile Gln Thr Gly Asn Gln
20 25 30

His Gln Ala Glu Pro Cys Asn Gln Ser Ile Ile Thr Tyr Glu Asn Asn
35 40 45

Thr Trp Val Asn Gln Thr Tyr Val Asn Ile Ser Asn Thr Asn Phe Leu
50 55 60

Thr Glu Lys Ala Val Ala Ser Val Thr Leu Ala Gly Asn Ser Ser Leu
65 70 75 80

Cys Pro Ile Ser Gly Trp Ala Val Tyr Ser Lys Asp Asn Gly Ile Arg
85 90 95

```
Ile Gly Ser Lys Gly Asp Val Phe Val Ile Arg Glu Pro Phe Ile Ser
            100                 105                 110

Cys Ser His Leu Glu Cys Arg Thr Phe Phe Leu Thr Gln Gly Ala Leu
        115                 120                 125

Leu Asn Asp Lys His Ser Asn Gly Thr Val Lys Asp Arg Ser Pro His
    130                 135                 140

Arg Thr Leu Met Ser Cys Pro Val Gly Glu Ala Pro Ser Pro Tyr Asn
145                 150                 155                 160

Ser Arg Phe Glu Ser Val Ala Trp Ser Ala Ser Ala Cys His Asp Gly
                165                 170                 175

Thr Ser Trp Leu Thr Ile Gly Ile Ser Gly Pro Asp Asn Gly Ala Val
            180                 185                 190

Ala Val Leu Lys Tyr Asn Gly Ile Ile Thr Asp Thr Ile Lys Ser Trp
        195                 200                 205

Arg Asn Asn Ile Met Arg Thr Gln Glu Ser Glu Cys Ala Cys Val Asn
    210                 215                 220

Gly Ser Cys Phe Thr Val Met Thr Asp Gly Pro Ser Asn Gly Gln Ala
225                 230                 235                 240

Ser Tyr Lys Ile Phe Arg Ile Glu Lys Gly Lys Val Val Lys Ser Ala
                245                 250                 255

Glu Leu Asn Ala Pro Asn Tyr His Tyr Glu Glu Cys Ser Cys Tyr Pro
            260                 265                 270

Asp Ala Gly Glu Ile Thr Cys Val Cys Arg Asp Asn Trp His Gly Ser
        275                 280                 285

Asn Arg Pro Trp Val Ser Phe Asn Gln Asn Leu Glu Tyr Arg Ile Gly
    290                 295                 300

Tyr Ile Cys Ser Gly Val Phe Gly Asp Asn Pro Arg Pro Asn Asp Gly
305                 310                 315                 320

Thr Gly Ser Cys Gly Pro Val Ser Pro Lys Gly Ala Tyr Gly Ile Lys
                325                 330                 335

Gly Phe Ser Phe Lys Tyr Gly Asn Gly Val Trp Ile Gly Arg Thr Lys
```

340 345 350

Ser Thr Asn Ser Arg Ser Gly Phe Glu Met Ile Trp Asp Pro Asn Gly
355 360 365

Trp Thr Gly Thr Asp Ser Asn Phe Ser Val Lys Gln Asp Ile Val Ala
370 375 380

Ile Thr Asp Trp Ser Gly Tyr Ser Gly Ser Phe Val Gln His Pro Glu
385 390 395 400

Leu Thr Gly Leu Asp Cys Ile Arg Pro Cys Phe Trp Val Glu Leu Ile
405 410 415

Arg Gly Arg Pro Lys Glu Ser Thr Ile Trp Thr Ser Gly Ser Ser Ile
420 425 430

Ser Phe Cys Gly Val Asn Ser Asp Thr Val Gly Trp Ser Trp Pro Asp
435 440 445

Gly Ala Glu Leu Pro Phe Thr Ile Asp Lys Gly Gly Gly Gly Ser Gly
450 455 460

Gly Gly Gly Ser Gly Gly Asp Ala His Lys Ser Glu Val Ala His Arg
465 470 475 480

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
485 490 495

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
500 505 510

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
515 520 525

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
530 535 540

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
545 550 555 560

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
565 570 575

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
580 585 590

```
Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
        595                 600                 605

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
    610                 615                 620

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
625                 630                 635                 640

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
                645                 650                 655

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
            660                 665                 670

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
        675                 680                 685

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
    690                 695                 700

Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
705                 710                 715                 720

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
                725                 730                 735

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
            740                 745                 750

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
        755                 760                 765

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
    770                 775                 780

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
785                 790                 795                 800

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
                805                 810                 815

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
            820                 825                 830

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
        835                 840                 845
```

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
850 855 860

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
865 870 875 880

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
885 890 895

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
900 905 910

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
915 920 925

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
930 935 940

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
945 950 955 960

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
965 970 975

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
980 985 990

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
995 1000 1005

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala
1010 1015 1020

Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
1025 1030 1035

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu
1040 1045 1050

Gly Leu
1055

<210> 667
<211> 1136
<212> PRT
<213> Artificial sequence

<220>

<223> HSA/Kex-2 signal sequence followed by a truncated form of hemagglutinin from Influenza A/Hong Kong/213/03 (HK213;H5N1)(amino acids 17-531) lacking a signal peptide and the C-terminal hydrophobic domain, fused via a Gly-Ser linker

<400> 667

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Gln Ile Cys Ile Gly Tyr His
            20                  25                  30

Ala Asn Asn Ser Thr Glu Gln Val Asp Thr Ile Met Glu Lys Asn Val
        35                  40                  45

Thr Val Thr His Ala Gln Asp Ile Leu Glu Lys Thr His Asn Gly Lys
    50                  55                  60

Leu Cys Asp Leu Asp Gly Val Lys Pro Leu Ile Leu Arg Asp Cys Ser
65                  70                  75                  80

Val Ala Gly Trp Leu Leu Gly Asn Pro Met Cys Asp Glu Phe Ile Asn
                85                  90                  95

Val Pro Glu Trp Ser Tyr Ile Val Glu Lys Ala Asn Pro Ala Asn Asp
            100                 105                 110

Leu Cys Tyr Pro Gly Asp Phe Asn Asp Tyr Glu Glu Leu Lys His Leu
        115                 120                 125

Leu Ser Arg Ile Asn His Phe Glu Lys Ile Gln Ile Ile Pro Lys Asn
    130                 135                 140

Ser Trp Ser Ser His Glu Ala Ser Leu Gly Val Ser Ser Ala Cys Pro
145                 150                 155                 160

Tyr Gln Gly Lys Ser Ser Phe Phe Arg Asn Val Val Trp Leu Ile Lys
                165                 170                 175

Lys Asn Asn Ala Tyr Pro Thr Ile Lys Arg Ser Tyr Asn Asn Thr Asn
            180                 185                 190

Gln Glu Asp Leu Leu Val Leu Trp Gly Ile His His Pro Asn Asp Ala
        195                 200                 205

Ala Glu Gln Thr Arg Leu Tyr Gln Asn Pro Thr Thr Tyr Ile Ser Val
    210                 215                 220
```

```
Gly Thr Ser Thr Leu Asn Gln Arg Leu Val Pro Lys Ile Ala Thr Arg
225                 230                 235                 240

Ser Lys Val Asn Gly Gln Asn Gly Arg Met Glu Phe Phe Trp Thr Ile
                245                 250                 255

Leu Lys Pro Asn Asp Ala Ile Asn Phe Glu Ser Asn Gly Asn Phe Ile
            260                 265                 270

Ala Pro Glu Tyr Ala Tyr Lys Ile Val Lys Lys Gly Asp Ser Ala Ile
        275                 280                 285

Met Lys Ser Glu Leu Glu Tyr Gly Asn Cys Asn Thr Lys Cys Gln Thr
    290                 295                 300

Pro Met Gly Ala Ile Asn Ser Ser Met Pro Phe His Asn Ile His Pro
305                 310                 315                 320

Leu Thr Ile Gly Glu Cys Pro Lys Tyr Val Lys Ser Asn Arg Leu Val
                325                 330                 335

Leu Ala Thr Gly Leu Arg Asn Ser Pro Gln Arg Glu Arg Arg Arg Lys
            340                 345                 350

Lys Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe Ile Glu Gly Gly Trp
        355                 360                 365

Gln Gly Met Val Asp Gly Trp Tyr Gly Tyr His His Ser Asn Glu Gln
    370                 375                 380

Gly Ser Gly Tyr Ala Ala Asp Lys Glu Ser Thr Gln Lys Ala Ile Asp
385                 390                 395                 400

Gly Val Thr Asn Lys Val Asn Ser Ile Ile Asp Lys Met Asn Thr Gln
                405                 410                 415

Phe Glu Ala Val Gly Arg Glu Phe Asn Asn Leu Glu Arg Arg Ile Glu
            420                 425                 430

Asn Leu Asn Lys Lys Met Glu Asp Gly Phe Leu Asp Val Trp Thr Tyr
        435                 440                 445

Asn Ala Glu Leu Leu Val Leu Met Glu Asn Glu Arg Thr Leu Asp Phe
    450                 455                 460

His Asp Ser Asn Val Lys Asn Leu Tyr Asp Lys Val Arg Leu Gln Leu
465                 470                 475                 480
```

Arg Asp Asn Ala Lys Glu Leu Gly Asn Gly Cys Phe Glu Phe Tyr His
485 490 495

Lys Cys Asp Asn Glu Cys Met Glu Ser Val Arg Asn Gly Thr Tyr Asp
500 505 510

Tyr Pro Gln Tyr Ser Glu Glu Ala Arg Leu Lys Arg Glu Glu Ile Ser
515 520 525

Gly Val Lys Leu Glu Ser Ile Gly Thr Tyr Gln Gly Gly Gly Gly Ser
530 535 540

Gly Gly Gly Gly Ser Gly Gly Asp Ala His Lys Ser Glu Val Ala His
545 550 555 560

Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile
565 570 575

Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys
580 585 590

Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu
595 600 605

Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
610 615 620

Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp
625 630 635 640

Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
645 650 655

Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp
660 665 670

Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys
675 680 685

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
690 695 700

Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys
705 710 715 720

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu

```
                725                 730                 735

Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala
            740                 745                 750

Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
        755                 760                 765

Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys
    770                 775                 780

Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp
785                 790                 795                 800

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
                805                 810                 815

Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys
            820                 825                 830

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu
        835                 840                 845

Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys
    850                 855                 860

Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met
865                 870                 875                 880

Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu
                885                 890                 895

Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys
            900                 905                 910

Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe
        915                 920                 925

Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu
    930                 935                 940

Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val
945                 950                 955                 960

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
                965                 970                 975
```

```
Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro
            980                 985                 990

Glu Ala Lys Arg Met Pro Cys Ala  Glu Asp Tyr Leu Ser  Val Val Leu
        995                 1000                1005

Asn Gln  Leu Cys Val Leu His  Glu Lys Thr Pro Val  Ser Asp Arg
    1010                1015                1020

Val Thr  Lys Cys Cys Thr Glu  Ser Leu Val Asn Arg  Arg Pro Cys
    1025                1030                1035

Phe Ser  Ala Leu Glu Val Asp  Glu Thr Tyr Val Pro  Lys Glu Phe
    1040                1045                1050

Asn Ala  Glu Thr Phe Thr Phe  His Ala Asp Ile Cys  Thr Leu Ser
    1055                1060                1065

Glu Lys  Glu Arg Gln Ile Lys  Lys Gln Thr Ala Leu  Val Glu Leu
    1070                1075                1080

Val Lys  His Lys Pro Lys Ala  Thr Lys Glu Gln Leu  Lys Ala Val
    1085                1090                1095

Met Asp  Asp Phe Ala Ala Phe  Val Glu Lys Cys Cys  Lys Ala Asp
    1100                1105                1110

Asp Lys  Glu Thr Cys Phe Ala  Glu Glu Gly Lys Lys  Leu Val Ala
    1115                1120                1125

Ala Ser  Gln Ala Ala Leu Gly  Leu
    1130                1135
```

<210> 668
<211> 1135
<212> PRT
<213> Artificial sequence

<220>
<223> A consensus signal sequence followed by a truncated form of hemagglutinin from Influenza A/Hong Kong/213/03 (HK213;H5N1) (amino acids 17-531) lacking a signal peptide and the C-terminal hydrophobic domain, fused via a Gly-Ser linker (GGGGSGGGGSGG) to

<400> 668

```
Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1               5                   10                  15

Leu Trp Ala Pro Ala Arg Gly Asp Gln Ile Cys Ile Gly Tyr His Ala
```

```
            20                  25                  30

Asn Asn Ser Thr Glu Gln Val Asp Thr Ile Met Glu Lys Asn Val Thr
        35                  40                  45

Val Thr His Ala Gln Asp Ile Leu Glu Lys Thr His Asn Gly Lys Leu
    50                  55                  60

Cys Asp Leu Asp Gly Val Lys Pro Leu Ile Leu Arg Asp Cys Ser Val
65                  70                  75                  80

Ala Gly Trp Leu Leu Gly Asn Pro Met Cys Asp Glu Phe Ile Asn Val
                85                  90                  95

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

Cys Tyr Pro Gly Asp Phe Asn Asp Tyr Glu Glu Leu Lys His Leu Leu
        115                 120                 125

Ser Arg Ile Asn His Phe Glu Lys Ile Gln Ile Ile Pro Lys Asn Ser
    130                 135                 140

Trp Ser Ser His Glu Ala Ser Leu Gly Val Ser Ser Ala Cys Pro Tyr
145                 150                 155                 160

Gln Gly Lys Ser Ser Phe Phe Arg Asn Val Val Trp Leu Ile Lys Lys
                165                 170                 175

Asn Asn Ala Tyr Pro Thr Ile Lys Arg Ser Tyr Asn Asn Thr Asn Gln
            180                 185                 190

Glu Asp Leu Leu Val Leu Trp Gly Ile His His Pro Asn Asp Ala Ala
        195                 200                 205

Glu Gln Thr Arg Leu Tyr Gln Asn Pro Thr Thr Tyr Ile Ser Val Gly
    210                 215                 220

Thr Ser Thr Leu Asn Gln Arg Leu Val Pro Lys Ile Ala Thr Arg Ser
225                 230                 235                 240

Lys Val Asn Gly Gln Asn Gly Arg Met Glu Phe Phe Trp Thr Ile Leu
                245                 250                 255

Lys Pro Asn Asp Ala Ile Asn Phe Glu Ser Asn Gly Asn Phe Ile Ala
            260                 265                 270
```

```
Pro Glu Tyr Ala Tyr Lys Ile Val Lys Lys Gly Asp Ser Ala Ile Met
        275                 280                 285

Lys Ser Glu Leu Glu Tyr Gly Asn Cys Asn Thr Lys Cys Gln Thr Pro
    290                 295                 300

Met Gly Ala Ile Asn Ser Ser Met Pro Phe His Asn Ile His Pro Leu
305                 310                 315                 320

Thr Ile Gly Glu Cys Pro Lys Tyr Val Lys Ser Asn Arg Leu Val Leu
                325                 330                 335

Ala Thr Gly Leu Arg Asn Ser Pro Gln Arg Glu Arg Arg Arg Lys Lys
            340                 345                 350

Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe Ile Glu Gly Gly Trp Gln
        355                 360                 365

Gly Met Val Asp Gly Trp Tyr Gly Tyr His His Ser Asn Glu Gln Gly
    370                 375                 380

Ser Gly Tyr Ala Ala Asp Lys Glu Ser Thr Gln Lys Ala Ile Asp Gly
385                 390                 395                 400

Val Thr Asn Lys Val Asn Ser Ile Ile Asp Lys Met Asn Thr Gln Phe
                405                 410                 415

Glu Ala Val Gly Arg Glu Phe Asn Asn Leu Glu Arg Arg Ile Glu Asn
            420                 425                 430

Leu Asn Lys Lys Met Glu Asp Gly Phe Leu Asp Val Trp Thr Tyr Asn
        435                 440                 445

Ala Glu Leu Leu Val Leu Met Glu Asn Glu Arg Thr Leu Asp Phe His
    450                 455                 460

Asp Ser Asn Val Lys Asn Leu Tyr Asp Lys Val Arg Leu Gln Leu Arg
465                 470                 475                 480

Asp Asn Ala Lys Glu Leu Gly Asn Gly Cys Phe Glu Phe Tyr His Lys
                485                 490                 495

Cys Asp Asn Glu Cys Met Glu Ser Val Arg Asn Gly Thr Tyr Asp Tyr
            500                 505                 510

Pro Gln Tyr Ser Glu Glu Ala Arg Leu Lys Arg Glu Glu Ile Ser Gly
        515                 520                 525
```

```
Val Lys Leu Glu Ser Ile Gly Thr Tyr Gln Gly Gly Gly Gly Ser Gly
    530                 535                 540

Gly Gly Gly Ser Gly Gly Asp Ala His Lys Ser Glu Val Ala His Arg
545                 550                 555                 560

Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala
                565                 570                 575

Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu
            580                 585                 590

Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
        595                 600                 605

Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
    610                 615                 620

Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys
625                 630                 635                 640

Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
                645                 650                 655

Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val
            660                 665                 670

Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr
        675                 680                 685

Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu
    690                 695                 700

Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln
705                 710                 715                 720

Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg
                725                 730                 735

Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser
            740                 745                 750

Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
        755                 760                 765

Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu
    770                 775                 780
```

```
Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu
785                 790                 795                 800

Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu
                805                 810                 815

Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro
            820                 825                 830

Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met
        835                 840                 845

Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp
    850                 855                 860

Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe
865                 870                 875                 880

Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu
                885                 890                 895

Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala
            900                 905                 910

Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys
        915                 920                 925

Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
    930                 935                 940

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
945                 950                 955                 960

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
                965                 970                 975

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
            980                 985                 990

Ala Lys Arg Met Pro Cys Ala Glu  Asp Tyr Leu Ser Val  Val Leu Asn
        995                 1000                1005

Gln Leu  Cys Val Leu His Glu  Lys Thr Pro Val Ser  Asp Arg Val
    1010                1015                1020

Thr Lys  Cys Cys Thr Glu Ser  Leu Val Asn Arg Arg  Pro Cys Phe
```

```
    1025                1030                1035

Ser Ala  Leu Glu Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Asn
    1040                1045                1050

Ala Glu  Thr Phe Thr Phe His  Ala Asp Ile Cys Thr  Leu Ser Glu
    1055                1060                1065

Lys Glu  Arg Gln Ile Lys Lys  Gln Thr Ala Leu Val  Glu Leu Val
    1070                1075                1080

Lys His  Lys Pro Lys Ala Thr  Lys Glu Gln Leu Lys  Ala Val Met
    1085                1090                1095

Asp Asp  Phe Ala Ala Phe Val  Glu Lys Cys Cys Lys  Ala Asp Asp
    1100                1105                1110

Lys Glu  Thr Cys Phe Ala Glu  Glu Gly Lys Lys Leu  Val Ala Ala
    1115                1120                1125

Ser Gln  Ala Ala Leu Gly Leu
    1130                1135
```

<210> 669
<211> 1138
<212> PRT
<213> Homo sapiens

<400> 669

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Glu Asp Asp Ile Ile Ile Ala Thr
            20                  25                  30

Lys Asn Gly Lys Val Arg Gly Met Gln Leu Thr Val Phe Gly Gly Thr
        35                  40                  45

Val Thr Ala Phe Leu Gly Ile Pro Tyr Ala Gln Pro Pro Leu Gly Arg
    50                  55                  60

Leu Arg Phe Lys Lys Pro Gln Ser Leu Thr Lys Trp Ser Asp Ile Trp
65                  70                  75                  80

Asn Ala Thr Lys Tyr Ala Asn Ser Cys Cys Gln Asn Ile Asp Gln Ser
                85                  90                  95

Phe Pro Gly Phe His Gly Ser Glu Met Trp Asn Pro Asn Thr Asp Leu
```

```
            100                 105                 110

Ser Glu Asp Cys Leu Tyr Leu Asn Val Trp Ile Pro Ala Pro Lys Pro
        115                 120                 125

Lys Asn Ala Thr Val Leu Ile Trp Ile Tyr Gly Gly Gly Phe Gln Thr
    130                 135                 140

Gly Thr Ser Ser Leu His Val Tyr Asp Gly Lys Phe Leu Ala Arg Val
145                 150                 155                 160

Glu Arg Val Ile Val Val Ser Met Asn Tyr Arg Val Gly Ala Leu Gly
                165                 170                 175

Phe Leu Ala Leu Pro Gly Asn Pro Glu Ala Pro Gly Asn Met Gly Leu
            180                 185                 190

Phe Asp Gln Gln Leu Ala Leu Gln Trp Val Gln Lys Asn Ile Ala Ala
        195                 200                 205

Phe Gly Gly Asn Pro Lys Ser Val Thr Leu Phe Gly Glu Ser Ala Gly
    210                 215                 220

Ala Ala Ser Val Ser Leu His Leu Leu Ser Pro Gly Ser His Ser Leu
225                 230                 235                 240

Phe Thr Arg Ala Ile Leu Gln Ser Gly Ser Phe Asn Ala Pro Trp Ala
                245                 250                 255

Val Thr Ser Leu Tyr Glu Ala Arg Asn Arg Thr Leu Asn Leu Ala Lys
            260                 265                 270

Leu Thr Gly Cys Ser Arg Glu Asn Glu Thr Glu Ile Ile Lys Cys Leu
        275                 280                 285

Arg Asn Lys Asp Pro Gln Glu Ile Leu Leu Asn Glu Ala Phe Val Val
    290                 295                 300

Pro Tyr Gly Thr Pro Leu Ser Val Asn Phe Gly Pro Thr Val Asp Gly
305                 310                 315                 320

Asp Phe Leu Thr Asp Met Pro Asp Ile Leu Leu Glu Leu Gly Gln Phe
                325                 330                 335

Lys Lys Thr Gln Ile Leu Val Gly Val Asn Lys Asp Glu Gly Thr Trp
            340                 345                 350
```

```
Phe Leu Val Ala Gly Ala Pro Gly Phe Ser Lys Asp Asn Asn Ser Ile
        355                 360                 365

Ile Thr Arg Lys Glu Phe Gln Glu Gly Leu Lys Ile Phe Phe Pro Gly
    370                 375                 380

Val Ser Glu Phe Gly Lys Glu Ser Ile Leu Phe His Tyr Thr Asp Trp
385                 390                 395                 400

Val Asp Asp Gln Arg Pro Glu Asn Tyr Arg Glu Ala Leu Gly Asp Val
                405                 410                 415

Val Gly Asp Tyr Asn Phe Ile Cys Pro Ala Leu Glu Phe Thr Lys Lys
            420                 425                 430

Phe Ser Glu Trp Gly Asn Asn Ala Phe Phe Tyr Tyr Phe Glu His Arg
        435                 440                 445

Ser Ser Lys Leu Pro Trp Pro Glu Trp Met Gly Val Met His Gly Tyr
    450                 455                 460

Glu Ile Glu Phe Val Phe Gly Leu Pro Leu Glu Arg Arg Asp Gln Tyr
465                 470                 475                 480

Thr Lys Ala Glu Glu Ile Leu Ser Arg Ser Ile Val Lys Arg Trp Ala
                485                 490                 495

Asn Phe Ala Lys Tyr Gly Asn Pro Gln Glu Thr Gln Asn Gln Ser Thr
            500                 505                 510

Ser Trp Pro Val Phe Lys Ser Thr Glu Gln Lys Tyr Leu Thr Leu Asn
        515                 520                 525

Thr Glu Ser Thr Arg Ile Met Thr Lys Leu Arg Ala Gln Gln Cys Arg
    530                 535                 540

Phe Trp Thr Ser Phe Phe Pro Lys Val Asp Ala His Lys Ser Glu Val
545                 550                 555                 560

Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val
                565                 570                 575

Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His
            580                 585                 590

Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala
        595                 600                 605
```

Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly
610 615 620

Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met
625 630 635 640

Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu
645 650 655

Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu
660 665 670

Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu
675 680 685

Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala
690 695 700

Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu
705 710 715 720

Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp
725 730 735

Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys
740 745 750

Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
755 760 765

Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val
770 775 780

Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His
785 790 795 800

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr
805 810 815

Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys
820 825 830

Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn
835 840 845

Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu
850 855 860

```
Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
865                 870                 875                 880

Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val
                885                 890                 895

Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys
            900                 905                 910

Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp
        915                 920                 925

Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn
    930                 935                 940

Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu
945                 950                 955                 960

Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu
                965                 970                 975

Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys
            980                 985                 990

His Pro Glu Ala Lys Arg Met Pro  Cys Ala Glu Asp Tyr  Leu Ser Val
        995                 1000                1005

Val Leu  Asn Gln Leu Cys Val  Leu His Glu Lys Thr  Pro Val Ser
    1010                1015                1020

Asp Arg  Val Thr Lys Cys Cys  Thr Glu Ser Leu Val  Asn Arg Arg
    1025                1030                1035

Pro Cys  Phe Ser Ala Leu Glu  Val Asp Glu Thr Tyr  Val Pro Lys
    1040                1045                1050

Glu Phe  Asn Ala Glu Thr Phe  Thr Phe His Ala Asp  Ile Cys Thr
    1055                1060                1065

Leu Ser  Glu Lys Glu Arg Gln  Ile Lys Lys Gln Thr  Ala Leu Val
    1070                1075                1080

Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Lys Glu  Gln Leu Lys
    1085                1090                1095

Ala Val  Met Asp Asp Phe Ala  Ala Phe Val Glu Lys  Cys Cys Lys
```

1100 1105 1110

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
1115 1120 1125

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
1130 1135

<210> 670
<211> 1137
<212> PRT
<213> Homo sapiens

<400> 670

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1 5 10 15

Leu Trp Ala Pro Ala Arg Gly Glu Asp Asp Ile Ile Ile Ala Thr Lys
20 25 30

Asn Gly Lys Val Arg Gly Met Gln Leu Thr Val Phe Gly Gly Thr Val
35 40 45

Thr Ala Phe Leu Gly Ile Pro Tyr Ala Gln Pro Pro Leu Gly Arg Leu
50 55 60

Arg Phe Lys Lys Pro Gln Ser Leu Thr Lys Trp Ser Asp Ile Trp Asn
65 70 75 80

Ala Thr Lys Tyr Ala Asn Ser Cys Cys Gln Asn Ile Asp Gln Ser Phe
85 90 95

Pro Gly Phe His Gly Ser Glu Met Trp Asn Pro Asn Thr Asp Leu Ser
100 105 110

Glu Asp Cys Leu Tyr Leu Asn Val Trp Ile Pro Ala Pro Lys Pro Lys
115 120 125

Asn Ala Thr Val Leu Ile Trp Ile Tyr Gly Gly Gly Phe Gln Thr Gly
130 135 140

Thr Ser Ser Leu His Val Tyr Asp Gly Lys Phe Leu Ala Arg Val Glu
145 150 155 160

Arg Val Ile Val Val Ser Met Asn Tyr Arg Val Gly Ala Leu Gly Phe
165 170 175

Leu Ala Leu Pro Gly Asn Pro Glu Ala Pro Gly Asn Met Gly Leu Phe

```
            180                 185                 190

Asp Gln Gln Leu Ala Leu Gln Trp Val Gln Lys Asn Ile Ala Ala Phe
        195                 200                 205

Gly Gly Asn Pro Lys Ser Val Thr Leu Phe Gly Glu Ser Ala Gly Ala
    210                 215                 220

Ala Ser Val Ser Leu His Leu Leu Ser Pro Gly Ser His Ser Leu Phe
225                 230                 235                 240

Thr Arg Ala Ile Leu Gln Ser Gly Ser Phe Asn Ala Pro Trp Ala Val
                245                 250                 255

Thr Ser Leu Tyr Glu Ala Arg Asn Arg Thr Leu Asn Leu Ala Lys Leu
            260                 265                 270

Thr Gly Cys Ser Arg Glu Asn Glu Thr Glu Ile Ile Lys Cys Leu Arg
        275                 280                 285

Asn Lys Asp Pro Gln Glu Ile Leu Leu Asn Glu Ala Phe Val Val Pro
    290                 295                 300

Tyr Gly Thr Pro Leu Ser Val Asn Phe Gly Pro Thr Val Asp Gly Asp
305                 310                 315                 320

Phe Leu Thr Asp Met Pro Asp Ile Leu Leu Glu Leu Gly Gln Phe Lys
                325                 330                 335

Lys Thr Gln Ile Leu Val Gly Val Asn Lys Asp Glu Gly Thr Trp Phe
            340                 345                 350

Leu Val Ala Gly Ala Pro Gly Phe Ser Lys Asp Asn Asn Ser Ile Ile
        355                 360                 365

Thr Arg Lys Glu Phe Gln Glu Gly Leu Lys Ile Phe Phe Pro Gly Val
    370                 375                 380

Ser Glu Phe Gly Lys Glu Ser Ile Leu Phe His Tyr Thr Asp Trp Val
385                 390                 395                 400

Asp Asp Gln Arg Pro Glu Asn Tyr Arg Glu Ala Leu Gly Asp Val Val
                405                 410                 415

Gly Asp Tyr Asn Phe Ile Cys Pro Ala Leu Glu Phe Thr Lys Lys Phe
            420                 425                 430
```

```
Ser Glu Trp Gly Asn Asn Ala Phe Phe Tyr Tyr Phe Glu His Arg Ser
        435                 440                 445

Ser Lys Leu Pro Trp Pro Glu Trp Met Gly Val Met His Gly Tyr Glu
    450                 455                 460

Ile Glu Phe Val Phe Gly Leu Pro Leu Glu Arg Arg Asp Gln Tyr Thr
465                 470                 475                 480

Lys Ala Glu Glu Ile Leu Ser Arg Ser Ile Val Lys Arg Trp Ala Asn
                485                 490                 495

Phe Ala Lys Tyr Gly Asn Pro Gln Glu Thr Gln Asn Gln Ser Thr Ser
            500                 505                 510

Trp Pro Val Phe Lys Ser Thr Glu Gln Lys Tyr Leu Thr Leu Asn Thr
        515                 520                 525

Glu Ser Thr Arg Ile Met Thr Lys Leu Arg Ala Gln Gln Cys Arg Phe
    530                 535                 540

Trp Thr Ser Phe Phe Pro Lys Val Asp Ala His Lys Ser Glu Val Ala
545                 550                 555                 560

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
                565                 570                 575

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
            580                 585                 590

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
        595                 600                 605

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
    610                 615                 620

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
625                 630                 635                 640

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
                645                 650                 655

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
            660                 665                 670

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
        675                 680                 685
```

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
690 695 700

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
705 710 715 720

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
725 730 735

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
740 745 750

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
755 760 765

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
770 775 780

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
785 790 795 800

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
805 810 815

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
820 825 830

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
835 840 845

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
850 855 860

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
865 870 875 880

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
885 890 895

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
900 905 910

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
915 920 925

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
930 935 940

```
Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
945                 950                 955                 960

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
                965                 970                 975

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
            980                 985                 990

Pro Glu Ala Lys Arg Met Pro Cys  Ala Glu Asp Tyr Leu  Ser Val Val
        995                 1000                1005

Leu Asn  Gln Leu Cys Val Leu  His Glu Lys Thr Pro  Val Ser Asp
    1010                1015                1020

Arg Val  Thr Lys Cys Cys Thr  Glu Ser Leu Val Asn  Arg Arg Pro
    1025                1030                1035

Cys Phe  Ser Ala Leu Glu Val  Asp Glu Thr Tyr Val  Pro Lys Glu
    1040                1045                1050

Phe Asn  Ala Glu Thr Phe Thr  Phe His Ala Asp Ile  Cys Thr Leu
    1055                1060                1065

Ser Glu  Lys Glu Arg Gln Ile  Lys Lys Gln Thr Ala  Leu Val Glu
    1070                1075                1080

Leu Val  Lys His Lys Pro Lys  Ala Thr Lys Glu Gln  Leu Lys Ala
    1085                1090                1095

Val Met  Asp Asp Phe Ala Ala  Phe Val Glu Lys Cys  Cys Lys Ala
    1100                1105                1110

Asp Asp  Lys Glu Thr Cys Phe  Ala Glu Glu Gly Lys  Lys Leu Val
    1115                1120                1125

Ala Ala  Ser Gln Ala Ala Leu  Gly Leu
    1130                1135
```

<210> 671
<211> 662
<212> PRT
<213> Homo sapiens

<400> 671

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15
```

```
Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
```

260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly
610 615 620

Cys Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr
625 630 635 640

Gln Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile
645 650 655

Ser Pro Gln Gly Tyr Gly
660

<210> 672
<211> 662
<212> PRT
<213> Homo sapiens

<400> 672

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

```
Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320
```

```
Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575
```

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly
610 615 620

Cys Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr
625 630 635 640

Gln Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile
645 650 655

Ser Pro Gln Gly Tyr Gly
660

<210> 673
<211> 678
<212> PRT
<213> Homo sapiens

<400> 673

Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

```
His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
```

```
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
    610                 615                 620
```

```
Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625                 630                 635                 640

Gln Arg Tyr Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
                645                 650                 655

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
            660                 665                 670

Thr Arg Gln Arg Tyr Gly
        675
```

<210> 674
<211> 678
<212> PRT
<213> Homo sapiens

<400> 674

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160
```

```
Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415
```

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
610 615 620

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625 630 635 640

Gln Arg Tyr Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
645 650 655

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
660 665 670

Thr Arg Gln Arg Tyr Gly
675

<210> 675
<211> 774
<212> PRT
<213> Homo sapiens

<400> 675

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Ser Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His

```
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
            660                 665                 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
        675                 680                 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700
```

```
Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705                 710                 715                 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770
```

<210> 676
<211> 774
<212> PRT
<213> Homo sapiens

<400> 676

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140
```

```
Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400
```

```
Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ser Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655
```

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 677
<211> 774
<212> PRT
<213> Homo sapiens

<400> 677

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

```
Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
```

```
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590
```

```
Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
    610                 615                 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Ser Leu Lys
625                 630                 635                 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
                645                 650                 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
            660                 665                 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
        675                 680                 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
    690                 695                 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705                 710                 715                 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
                725                 730                 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
            740                 745                 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
        755                 760                 765

Ser Leu Arg Ser Lys Glu
    770


<210>  678
<211>  774
<212>  PRT
<213>  Homo sapiens

<400>  678

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30
```

```
His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285
```

```
Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540
```

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Ser Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 679

<211> 774
<212> PRT
<213> Homo sapiens

<400> 679

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val

225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu
610 615 620

Met Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys
625 630 635 640

Asp Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe
645 650 655

Gln Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile
660 665 670

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
675 680 685

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
690 695 700

Glu Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met
705 710 715 720

Lys Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
725 730 735

Leu Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Ser Ala Trp Glu Val Val
740 745 750

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu
755 760 765

Ser Leu Arg Ser Lys Glu
770

<210> 680
<211> 397
<212> PRT
<213> Homo sapiens

<400> 680

Met Ala Pro Ile Ser Leu Ser Trp Leu Leu Arg Leu Ala Thr Phe Cys
1 5 10 15

His Leu Thr Val Leu Leu Ala Gly Gln His His Gly Val Thr Lys Cys
20 25 30

Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
35 40 45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
50 55 60

Leu Glu Thr Arg Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln
65 70 75 80

Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
85 90 95

Thr Arg Asn Gly Gly Thr Phe Glu Lys Gln Ile Gly Glu Val Lys Pro
100 105 110

Arg Thr Thr Pro Ala Ala Gly Gly Met Asp Glu Ser Val Val Leu Glu
115 120 125

Pro Glu Ala Thr Gly Glu Ser Ser Ser Leu Glu Pro Thr Pro Ser Ser
130 135 140

Gln Glu Ala Gln Arg Ala Leu Gly Thr Ser Pro Glu Leu Pro Thr Gly
145 150 155 160

Val Thr Gly Ser Ser Gly Thr Arg Leu Pro Pro Thr Pro Lys Ala Gln
165 170 175

```
Asp Gly Gly Pro Val Gly Thr Glu Leu Phe Arg Val Pro Pro Val Ser
            180                 185                 190

Thr Ala Ala Thr Trp Gln Ser Ser Ala Pro His Gln Pro Gly Pro Ser
        195                 200                 205

Leu Trp Ala Glu Ala Lys Thr Ser Glu Ala Pro Ser Thr Gln Asp Pro
    210                 215                 220

Ser Thr Gln Ala Ser Thr Ala Ser Ser Pro Ala Pro Glu Glu Asn Ala
225                 230                 235                 240

Pro Ser Glu Gly Gln Arg Val Trp Gly Gln Gly Gln Ser Pro Arg Pro
                245                 250                 255

Glu Asn Ser Leu Glu Arg Glu Glu Met Gly Pro Val Pro Ala His Thr
            260                 265                 270

Asp Ala Phe Gln Asp Trp Gly Pro Gly Ser Met Ala His Val Ser Val
        275                 280                 285

Val Pro Val Ser Ser Glu Gly Thr Pro Ser Arg Glu Pro Val Ala Ser
    290                 295                 300

Gly Ser Trp Thr Pro Lys Ala Glu Glu Pro Ile His Ala Thr Met Asp
305                 310                 315                 320

Pro Gln Arg Leu Gly Val Leu Ile Thr Pro Val Pro Asp Ala Gln Ala
                325                 330                 335

Ala Thr Arg Arg Gln Ala Val Gly Leu Leu Ala Phe Leu Gly Leu Leu
            340                 345                 350

Phe Cys Leu Gly Val Ala Met Phe Thr Tyr Gln Ser Leu Gln Gly Cys
        355                 360                 365

Pro Arg Lys Met Ala Gly Glu Met Ala Glu Gly Leu Arg Tyr Ile Pro
    370                 375                 380

Arg Ser Cys Gly Ser Asn Ser Tyr Val Leu Val Pro Val
385                 390                 395


<210>  681
<211>  397
<212>  PRT
<213>  Homo sapiens

<400>  681
```

```
Met Ala Pro Ile Ser Leu Ser Trp Leu Leu Arg Leu Ala Thr Phe Cys
1               5                   10                  15

His Leu Thr Val Leu Leu Ala Gly Gln His His Gly Val Thr Lys Cys
            20                  25                  30

Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
        35                  40                  45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
    50                  55                  60

Leu Glu Thr Arg Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln
65                  70                  75                  80

Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
                85                  90                  95

Thr Arg Asn Gly Gly Thr Phe Glu Lys Gln Ile Gly Glu Val Lys Pro
            100                 105                 110

Arg Thr Thr Pro Ala Ala Gly Gly Met Asp Glu Ser Val Val Leu Glu
        115                 120                 125

Pro Glu Ala Thr Gly Glu Ser Ser Ser Leu Glu Pro Thr Pro Ser Ser
    130                 135                 140

Gln Glu Ala Gln Arg Ala Leu Gly Thr Ser Pro Glu Leu Pro Thr Gly
145                 150                 155                 160

Val Thr Gly Ser Ser Gly Thr Arg Leu Pro Pro Thr Pro Lys Ala Gln
                165                 170                 175

Asp Gly Gly Pro Val Gly Thr Glu Leu Phe Arg Val Pro Pro Val Ser
            180                 185                 190

Thr Ala Ala Thr Trp Gln Ser Ser Ala Pro His Gln Pro Gly Pro Ser
        195                 200                 205

Leu Trp Ala Glu Ala Lys Thr Ser Glu Ala Pro Ser Thr Gln Asp Pro
    210                 215                 220

Ser Thr Gln Ala Ser Thr Ala Ser Ser Pro Ala Pro Glu Glu Asn Ala
225                 230                 235                 240

Pro Ser Glu Gly Gln Arg Val Trp Gly Gln Gly Gln Ser Pro Arg Pro
                245                 250                 255
```

```
Glu Asn Ser Leu Glu Arg Glu Glu Met Gly Pro Val Pro Ala His Thr
            260                 265                 270

Asp Ala Phe Gln Asp Trp Gly Pro Gly Ser Met Ala His Val Ser Val
        275                 280                 285

Val Pro Val Ser Ser Glu Gly Thr Pro Ser Arg Glu Pro Val Ala Ser
    290                 295                 300

Gly Ser Trp Thr Pro Lys Ala Glu Glu Pro Ile His Ala Thr Met Asp
305                 310                 315                 320

Pro Gln Arg Leu Gly Val Leu Ile Thr Pro Val Pro Asp Ala Gln Ala
                325                 330                 335

Ala Thr Arg Arg Gln Ala Val Gly Leu Leu Ala Phe Leu Gly Leu Leu
            340                 345                 350

Phe Cys Leu Gly Val Ala Met Phe Thr Tyr Gln Ser Leu Gln Gly Cys
        355                 360                 365

Pro Arg Lys Met Ala Gly Glu Met Ala Glu Gly Leu Arg Tyr Ile Pro
    370                 375                 380

Arg Ser Cys Gly Ser Asn Ser Tyr Val Leu Val Pro Val
385                 390                 395


<210>  682
<211>  397
<212>  PRT
<213>  Homo sapiens

<400>  682

Met Ala Pro Ile Ser Leu Ser Trp Leu Leu Arg Leu Ala Thr Phe Cys
1               5                   10                  15

His Leu Thr Val Leu Leu Ala Gly Gln His His Gly Val Thr Lys Cys
            20                  25                  30

Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
        35                  40                  45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
    50                  55                  60

Leu Glu Thr Arg Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln
65                  70                  75                  80
```

```
Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
                85                  90                  95

Thr Arg Asn Gly Gly Thr Phe Glu Lys Gln Ile Gly Glu Val Lys Pro
            100                 105                 110

Arg Thr Thr Pro Ala Ala Gly Gly Met Asp Glu Ser Val Val Leu Glu
        115                 120                 125

Pro Glu Ala Thr Gly Glu Ser Ser Ser Leu Glu Pro Thr Pro Ser Ser
    130                 135                 140

Gln Glu Ala Gln Arg Ala Leu Gly Thr Ser Pro Glu Leu Pro Thr Gly
145                 150                 155                 160

Val Thr Gly Ser Ser Gly Thr Arg Leu Pro Pro Thr Pro Lys Ala Gln
                165                 170                 175

Asp Gly Gly Pro Val Gly Thr Glu Leu Phe Arg Val Pro Pro Val Ser
            180                 185                 190

Thr Ala Ala Thr Trp Gln Ser Ser Ala Pro His Gln Pro Gly Pro Ser
        195                 200                 205

Leu Trp Ala Glu Ala Lys Thr Ser Glu Ala Pro Ser Thr Gln Asp Pro
    210                 215                 220

Ser Thr Gln Ala Ser Thr Ala Ser Ser Pro Ala Pro Glu Glu Asn Ala
225                 230                 235                 240

Pro Ser Glu Gly Gln Arg Val Trp Gly Gln Gly Gln Ser Pro Arg Pro
                245                 250                 255

Glu Asn Ser Leu Glu Arg Glu Glu Met Gly Pro Val Pro Ala His Thr
            260                 265                 270

Asp Ala Phe Gln Asp Trp Gly Pro Gly Ser Met Ala His Val Ser Val
        275                 280                 285

Val Pro Val Ser Ser Glu Gly Thr Pro Ser Arg Glu Pro Val Ala Ser
    290                 295                 300

Gly Ser Trp Thr Pro Lys Ala Glu Glu Pro Ile His Ala Thr Met Asp
305                 310                 315                 320

Pro Gln Arg Leu Gly Val Leu Ile Thr Pro Val Pro Asp Ala Gln Ala
```

325 330 335

Ala Thr Arg Arg Gln Ala Val Gly Leu Leu Ala Phe Leu Gly Leu Leu
340 345 350

Phe Cys Leu Gly Val Ala Met Phe Thr Tyr Gln Ser Leu Gln Gly Cys
355 360 365

Pro Arg Lys Met Ala Gly Glu Met Ala Glu Gly Leu Arg Tyr Ile Pro
370 375 380

Arg Ser Cys Gly Ser Asn Ser Tyr Val Leu Val Pro Val
385 390 395

<210> 683
<211> 397
<212> PRT
<213> Homo sapiens

<400> 683

Met Ala Pro Ile Ser Leu Ser Trp Leu Leu Arg Leu Ala Thr Phe Cys
1 5 10 15

His Leu Thr Val Leu Leu Ala Gly Gln His His Gly Val Thr Lys Cys
20 25 30

Asn Ile Thr Cys Ser Lys Met Thr Ser Lys Ile Pro Val Ala Leu Leu
35 40 45

Ile His Tyr Gln Gln Asn Gln Ala Ser Cys Gly Lys Arg Ala Ile Ile
50 55 60

Leu Glu Thr Arg Gln His Arg Leu Phe Cys Ala Asp Pro Lys Glu Gln
65 70 75 80

Trp Val Lys Asp Ala Met Gln His Leu Asp Arg Gln Ala Ala Ala Leu
85 90 95

Thr Arg Asn Gly Gly Thr Phe Glu Lys Gln Ile Gly Glu Val Lys Pro
100 105 110

Arg Thr Thr Pro Ala Ala Gly Gly Met Asp Glu Ser Val Val Leu Glu
115 120 125

Pro Glu Ala Thr Gly Glu Ser Ser Ser Leu Glu Pro Thr Pro Ser Ser
130 135 140

Gln Glu Ala Gln Arg Ala Leu Gly Thr Ser Pro Glu Leu Pro Thr Gly

```
145                 150                 155                 160

Val Thr Gly Ser Ser Gly Thr Arg Leu Pro Pro Thr Pro Lys Ala Gln
                165                 170                 175

Asp Gly Gly Pro Val Gly Thr Glu Leu Phe Arg Val Pro Pro Val Ser
            180                 185                 190

Thr Ala Ala Thr Trp Gln Ser Ser Ala Pro His Gln Pro Gly Pro Ser
        195                 200                 205

Leu Trp Ala Glu Ala Lys Thr Ser Glu Ala Pro Ser Thr Gln Asp Pro
    210                 215                 220

Ser Thr Gln Ala Ser Thr Ala Ser Ser Pro Ala Pro Glu Glu Asn Ala
225                 230                 235                 240

Pro Ser Glu Gly Gln Arg Val Trp Gly Gln Gly Gln Ser Pro Arg Pro
                245                 250                 255

Glu Asn Ser Leu Glu Arg Glu Glu Met Gly Pro Val Pro Ala His Thr
            260                 265                 270

Asp Ala Phe Gln Asp Trp Gly Pro Gly Ser Met Ala His Val Ser Val
        275                 280                 285

Val Pro Val Ser Ser Glu Gly Thr Pro Ser Arg Glu Pro Val Ala Ser
    290                 295                 300

Gly Ser Trp Thr Pro Lys Ala Glu Glu Pro Ile His Ala Thr Met Asp
305                 310                 315                 320

Pro Gln Arg Leu Gly Val Leu Ile Thr Pro Val Pro Asp Ala Gln Ala
                325                 330                 335

Ala Thr Arg Arg Gln Ala Val Gly Leu Leu Ala Phe Leu Gly Leu Leu
            340                 345                 350

Phe Cys Leu Gly Val Ala Met Phe Thr Tyr Gln Ser Leu Gln Gly Cys
        355                 360                 365

Pro Arg Lys Met Ala Gly Glu Met Ala Glu Gly Leu Arg Tyr Ile Pro
    370                 375                 380

Arg Ser Cys Gly Ser Asn Ser Tyr Val Leu Val Pro Val
385                 390                 395
```

<210> 684
<211> 37
<212> PRT
<213> Homo sapiens

<400> 684

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile Ala
35

<210> 685
<211> 37
<212> PRT
<213> Homo sapiens

<400> 685

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile Ala
35

<210> 686
<211> 37
<212> PRT
<213> Homo sapiens

<400> 686

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile Ala
35

<210> 687
<211> 10
<212> PRT
<213> Pichia anomala

<400> 687

```
Ala Lys Val Thr Met Thr Cys Ser Ala Ser
1               5                   10


<210>  688
<211>  37
<212>  PRT
<213>  Homo sapiens

<400>  688

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1               5                   10                  15


Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
            20                  25                  30


Arg Asn Asn Ile Ala
        35


<210>  689
<211>  224
<212>  PRT
<213>  Homo sapiens

<400>  689

Met Pro Gly Ser Pro Arg Pro Ala Pro Ser Trp Val Leu Leu Leu Arg
1               5                   10                  15


Leu Leu Ala Leu Leu Arg Pro Pro Gly Leu Gly Glu Ala Cys Ser Cys
            20                  25                  30


Ala Pro Ala His Pro Gln Gln His Ile Cys His Ser Ala Leu Val Ile
        35                  40                  45


Arg Ala Lys Ile Ser Ser Glu Lys Val Val Pro Ala Ser Ala Asp Pro
    50                  55                  60


Ala Asp Thr Glu Lys Met Leu Arg Tyr Glu Ile Lys Gln Ile Lys Met
65                  70                  75                  80


Phe Lys Gly Phe Glu Lys Val Lys Asp Val Gln Tyr Ile Tyr Thr Pro
                85                  90                  95


Phe Asp Ser Ser Leu Cys Gly Val Lys Leu Glu Ala Asn Ser Gln Lys
            100                 105                 110


Gln Tyr Leu Leu Thr Gly Gln Val Leu Ser Asp Gly Lys Val Phe Ile
        115                 120                 125
```

```
His Leu Cys Asn Tyr Ile Glu Pro Trp Glu Asp Leu Ser Leu Val Gln
    130                 135                 140

Arg Glu Ser Leu Asn His His Tyr His Leu Asn Cys Gly Cys Gln Ile
145                 150                 155                 160

Thr Thr Cys Tyr Thr Val Pro Cys Thr Ile Ser Ala Pro Asn Glu Cys
                165                 170                 175

Leu Trp Thr Asp Trp Leu Leu Glu Arg Lys Leu Tyr Gly Tyr Gln Ala
            180                 185                 190

Gln His Tyr Val Cys Met Lys His Val Asp Gly Thr Cys Ser Trp Tyr
        195                 200                 205

Arg Gly His Leu Pro Leu Arg Lys Glu Phe Val Asp Ile Val Gln Pro
    210                 215                 220
```

<210> 690
<211> 224
<212> PRT
<213> Homo sapiens

<400> 690

```
Met Pro Gly Ser Pro Arg Pro Ala Pro Ser Trp Val Leu Leu Leu Arg
1               5                   10                  15

Leu Leu Ala Leu Leu Arg Pro Pro Gly Leu Gly Glu Ala Cys Ser Cys
            20                  25                  30

Ala Pro Ala His Pro Gln Gln His Ile Cys His Ser Ala Leu Val Ile
        35                  40                  45

Arg Ala Lys Ile Ser Ser Glu Lys Val Val Pro Ala Ser Ala Asp Pro
    50                  55                  60

Ala Asp Thr Glu Lys Met Leu Arg Tyr Glu Ile Lys Gln Ile Lys Met
65                  70                  75                  80

Phe Lys Gly Phe Glu Lys Val Lys Asp Val Gln Tyr Ile Tyr Thr Pro
                85                  90                  95

Phe Asp Ser Ser Leu Cys Gly Val Lys Leu Glu Ala Asn Ser Gln Lys
            100                 105                 110

Gln Tyr Leu Leu Thr Gly Gln Val Leu Ser Asp Gly Lys Val Phe Ile
        115                 120                 125
```

```
His Leu Cys Asn Tyr Ile Glu Pro Trp Glu Asp Leu Ser Leu Val Gln
    130                 135                 140

Arg Glu Ser Leu Asn His His Tyr His Leu Asn Cys Gly Cys Gln Ile
145                 150                 155                 160

Thr Thr Cys Tyr Thr Val Pro Cys Thr Ile Ser Ala Pro Asn Glu Cys
                165                 170                 175

Leu Trp Thr Asp Trp Leu Leu Glu Arg Lys Leu Tyr Gly Tyr Gln Ala
            180                 185                 190

Gln His Tyr Val Cys Met Lys His Val Asp Gly Thr Cys Ser Trp Tyr
        195                 200                 205

Arg Gly His Leu Pro Leu Arg Lys Glu Phe Val Asp Ile Val Gln Pro
    210                 215                 220
```

<210> 691
<211> 36
<212> PRT
<213> Homo sapiens

<400> 691

```
Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1               5                   10                  15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
            20                  25                  30

Arg Gln Arg Tyr
        35
```

<210> 692
<211> 36
<212> PRT
<213> Homo sapiens

<400> 692

```
Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1               5                   10                  15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
            20                  25                  30

Arg Gln Arg Tyr
        35
```

<210> 693

<211> 52
<212> PRT
<213> Homo sapiens

<400> 693

Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 694
<211> 36
<212> PRT
<213> Homo sapiens

<400> 694

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile
35

<210> 695
<211> 28
<212> PRT
<213> Homo sapiens

<400> 695

Gly Ser Ser Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys
1 5 10 15

Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro Arg
20 25

<210> 696
<211> 28
<212> PRT
<213> Homo sapiens

<400> 696

Gly Ser Ser Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys
1 5 10 15

Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro Arg
20 25

<210> 697
<211> 37
<212> PRT
<213> Homo sapiens

<400> 697

Ala Cys Asp Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> 698
<211> 37
<212> PRT
<213> Homo sapiens

<400> 698

Ala Cys Asp Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> 699
<211> 37
<212> PRT
<213> Homo sapiens

<400> 699

Ala Cys Asp Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> 700
<211> 37
<212> PRT
<213> Homo sapiens

<400> 700

Ala Cys Asp Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> 701
<211> 153
<212> PRT
<213> Homo sapiens

<400> 701

Met Gly Lys Ile Ser Ser Leu Pro Thr Gln Leu Phe Lys Cys Cys Phe
1 5 10 15

Cys Asp Phe Leu Lys Val Lys Met His Thr Met Ser Ser Ser His Leu
20 25 30

Phe Tyr Leu Ala Leu Cys Leu Leu Thr Phe Thr Ser Ser Ala Thr Ala
35 40 45

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
50 55 60

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
65 70 75 80

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
85 90 95

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
100 105 110

Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
115 120 125

Met Pro Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly
130 135 140

Ser Ala Gly Asn Lys Asn Tyr Arg Met
145 150

<210> 702
<211> 153
<212> PRT
<213> Homo sapiens

<400> 702

Met Gly Lys Ile Ser Ser Leu Pro Thr Gln Leu Phe Lys Cys Cys Phe
1 5 10 15

Cys Asp Phe Leu Lys Val Lys Met His Thr Met Ser Ser Ser His Leu
20 25 30

Phe Tyr Leu Ala Leu Cys Leu Leu Thr Phe Thr Ser Ser Ala Thr Ala
35 40 45

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
50 55 60

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
65 70 75 80

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
85 90 95

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
100 105 110

Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
115 120 125

Met Pro Lys Thr Gln Lys Glu Val His Leu Lys Asn Ala Ser Arg Gly
130 135 140

Ser Ala Gly Asn Lys Asn Tyr Arg Met
145 150

<210> 703
<211> 36
<212> PRT
<213> Homo sapiens

<400> 703

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile
35

<210> 704
<211> 469
<212> PRT
<213> Influenza A virus

<400> 704

Met Asn Pro Asn Gln Lys Ile Thr Thr Ile Gly Ser Ile Cys Met Val
1 5 10 15

Ile Gly Ile Val Ser Leu Met Leu Gln Ile Gly Asn Ile Ile Ser Ile
20 25 30

Trp Val Ser His Ser Ile Gln Thr Gly Asn Gln His Gln Ala Glu Pro
35 40 45

Cys Asn Gln Ser Ile Ile Thr Tyr Glu Asn Asn Thr Trp Val Asn Gln
50 55 60

Thr Tyr Val Asn Ile Ser Asn Thr Asn Phe Leu Thr Glu Lys Ala Val
65 70 75 80

Ala Ser Val Thr Leu Ala Gly Asn Ser Ser Leu Cys Pro Ile Ser Gly
85 90 95

Trp Ala Val Tyr Ser Lys Asp Asn Gly Ile Arg Ile Gly Ser Lys Gly
100 105 110

Asp Val Phe Val Ile Arg Glu Pro Phe Ile Ser Cys Ser His Leu Glu
115 120 125

Cys Arg Thr Phe Phe Leu Thr Gln Gly Ala Leu Leu Asn Asp Lys His
130 135 140

Ser Asn Gly Thr Val Lys Asp Arg Ser Pro His Arg Thr Leu Met Ser
145 150 155 160

Cys Pro Val Gly Glu Ala Pro Ser Pro Tyr Asn Ser Arg Phe Glu Ser
165 170 175

Val Ala Trp Ser Ala Ser Ala Cys His Asp Gly Thr Ser Trp Leu Thr
180 185 190

```
Ile Gly Ile Ser Gly Pro Asp Asn Gly Ala Val Ala Val Leu Lys Tyr
        195                 200                 205

Asn Gly Ile Ile Thr Asp Thr Ile Lys Ser Trp Arg Asn Asn Ile Met
    210                 215                 220

Arg Thr Gln Glu Ser Glu Cys Ala Cys Val Asn Gly Ser Cys Phe Thr
225                 230                 235                 240

Val Met Thr Asp Gly Pro Ser Asn Gly Gln Ala Ser Tyr Lys Ile Phe
                245                 250                 255

Arg Ile Glu Lys Gly Lys Val Val Lys Ser Ala Glu Leu Asn Ala Pro
            260                 265                 270

Asn Tyr His Tyr Glu Glu Cys Ser Cys Tyr Pro Asp Ala Gly Glu Ile
        275                 280                 285

Thr Cys Val Cys Arg Asp Asn Trp His Gly Ser Asn Arg Pro Trp Val
    290                 295                 300

Ser Phe Asn Gln Asn Leu Glu Tyr Arg Ile Gly Tyr Ile Cys Ser Gly
305                 310                 315                 320

Val Phe Gly Asp Asn Pro Arg Pro Asn Asp Gly Thr Gly Ser Cys Gly
                325                 330                 335

Pro Val Ser Pro Lys Gly Ala Tyr Gly Ile Lys Gly Phe Ser Phe Lys
            340                 345                 350

Tyr Gly Asn Gly Val Trp Ile Gly Arg Thr Lys Ser Thr Asn Ser Arg
        355                 360                 365

Ser Gly Phe Glu Met Ile Trp Asp Pro Asn Gly Trp Thr Gly Thr Asp
    370                 375                 380

Ser Asn Phe Ser Val Lys Gln Asp Ile Val Ala Ile Thr Asp Trp Ser
385                 390                 395                 400

Gly Tyr Ser Gly Ser Phe Val Gln His Pro Glu Leu Thr Gly Leu Asp
                405                 410                 415

Cys Ile Arg Pro Cys Phe Trp Val Glu Leu Ile Arg Gly Arg Pro Lys
            420                 425                 430

Glu Ser Thr Ile Trp Thr Ser Gly Ser Ser Ile Ser Phe Cys Gly Val
        435                 440                 445
```

```
Asn Ser Asp Thr Val Gly Trp Ser Trp Pro Asp Gly Ala Glu Leu Pro
    450                 455                 460

Phe Thr Ile Asp Lys
465
```

<210> 705
<211> 469
<212> PRT
<213> Influenza A virus

<400> 705

```
Met Asn Pro Asn Gln Lys Ile Thr Thr Ile Gly Ser Ile Cys Met Val
1               5                  10                  15

Ile Gly Ile Val Ser Leu Met Leu Gln Ile Gly Asn Ile Ile Ser Ile
            20                  25                  30

Trp Val Ser His Ser Ile Gln Thr Gly Asn Gln His Gln Ala Glu Pro
        35                  40                  45

Cys Asn Gln Ser Ile Ile Thr Tyr Glu Asn Asn Thr Trp Val Asn Gln
    50                  55                  60

Thr Tyr Val Asn Ile Ser Asn Thr Asn Phe Leu Thr Glu Lys Ala Val
65                  70                  75                  80

Ala Ser Val Thr Leu Ala Gly Asn Ser Ser Leu Cys Pro Ile Ser Gly
                85                  90                  95

Trp Ala Val Tyr Ser Lys Asp Asn Gly Ile Arg Ile Gly Ser Lys Gly
            100                 105                 110

Asp Val Phe Val Ile Arg Glu Pro Phe Ile Ser Cys Ser His Leu Glu
        115                 120                 125

Cys Arg Thr Phe Phe Leu Thr Gln Gly Ala Leu Leu Asn Asp Lys His
    130                 135                 140

Ser Asn Gly Thr Val Lys Asp Arg Ser Pro His Arg Thr Leu Met Ser
145                 150                 155                 160

Cys Pro Val Gly Glu Ala Pro Ser Pro Tyr Asn Ser Arg Phe Glu Ser
                165                 170                 175

Val Ala Trp Ser Ala Ser Ala Cys His Asp Gly Thr Ser Trp Leu Thr
            180                 185                 190
```

```
Ile Gly Ile Ser Gly Pro Asp Asn Gly Ala Val Ala Val Leu Lys Tyr
        195                 200                 205

Asn Gly Ile Ile Thr Asp Thr Ile Lys Ser Trp Arg Asn Asn Ile Met
    210                 215                 220

Arg Thr Gln Glu Ser Glu Cys Ala Cys Val Asn Gly Ser Cys Phe Thr
225                 230                 235                 240

Val Met Thr Asp Gly Pro Ser Asn Gly Gln Ala Ser Tyr Lys Ile Phe
                245                 250                 255

Arg Ile Glu Lys Gly Lys Val Val Lys Ser Ala Glu Leu Asn Ala Pro
            260                 265                 270

Asn Tyr His Tyr Glu Glu Cys Ser Cys Tyr Pro Asp Ala Gly Glu Ile
        275                 280                 285

Thr Cys Val Cys Arg Asp Asn Trp His Gly Ser Asn Arg Pro Trp Val
    290                 295                 300

Ser Phe Asn Gln Asn Leu Glu Tyr Arg Ile Gly Tyr Ile Cys Ser Gly
305                 310                 315                 320

Val Phe Gly Asp Asn Pro Arg Pro Asn Asp Gly Thr Gly Ser Cys Gly
                325                 330                 335

Pro Val Ser Pro Lys Gly Ala Tyr Gly Ile Lys Gly Phe Ser Phe Lys
            340                 345                 350

Tyr Gly Asn Gly Val Trp Ile Gly Arg Thr Lys Ser Thr Asn Ser Arg
        355                 360                 365

Ser Gly Phe Glu Met Ile Trp Asp Pro Asn Gly Trp Thr Gly Thr Asp
    370                 375                 380

Ser Asn Phe Ser Val Lys Gln Asp Ile Val Ala Ile Thr Asp Trp Ser
385                 390                 395                 400

Gly Tyr Ser Gly Ser Phe Val Gln His Pro Glu Leu Thr Gly Leu Asp
                405                 410                 415

Cys Ile Arg Pro Cys Phe Trp Val Glu Leu Ile Arg Gly Arg Pro Lys
            420                 425                 430

Glu Ser Thr Ile Trp Thr Ser Gly Ser Ser Ile Ser Phe Cys Gly Val
        435                 440                 445
```

```
Asn Ser Asp Thr Val Gly Trp Ser Trp Pro Asp Gly Ala Glu Leu Pro
    450                 455                 460

Phe Thr Ile Asp Lys
465
```

<210> 706
<211> 568
<212> PRT
<213> Influenza A virus

<400> 706

```
Met Glu Lys Ile Val Leu Leu Phe Ala Ile Val Ser Leu Val Lys Ser
1               5                   10                  15

Asp Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Gln Val
            20                  25                  30

Asp Thr Ile Met Glu Lys Asn Val Thr Val Thr His Ala Gln Asp Ile
        35                  40                  45

Leu Glu Lys Thr His Asn Gly Lys Leu Cys Asp Leu Asp Gly Val Lys
    50                  55                  60

Pro Leu Ile Leu Arg Asp Cys Ser Val Ala Gly Trp Leu Leu Gly Asn
65                  70                  75                  80

Pro Met Cys Asp Glu Phe Ile Asn Val Pro Glu Trp Ser Tyr Ile Val
                85                  90                  95

Glu Lys Ala Asn Pro Ala Asn Asp Leu Cys Tyr Pro Gly Asp Phe Asn
            100                 105                 110

Asp Tyr Glu Glu Leu Lys His Leu Leu Ser Arg Ile Asn His Phe Glu
        115                 120                 125

Lys Ile Gln Ile Ile Pro Lys Asn Ser Trp Ser Ser His Glu Ala Ser
    130                 135                 140

Leu Gly Val Ser Ser Ala Cys Pro Tyr Gln Gly Lys Ser Ser Phe Phe
145                 150                 155                 160

Arg Asn Val Val Trp Leu Ile Lys Lys Asn Asn Ala Tyr Pro Thr Ile
                165                 170                 175

Lys Arg Ser Tyr Asn Asn Thr Asn Gln Glu Asp Leu Leu Val Leu Trp
            180                 185                 190
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Gly Ile His His Pro Asn Asp Ala Ala Glu Gln Thr Arg Leu Tyr Gln
        195                 200                 205

Asn Pro Thr Thr Tyr Ile Ser Val Gly Thr Ser Thr Leu Asn Gln Arg
    210                 215                 220

Leu Val Pro Lys Ile Ala Thr Arg Ser Lys Val Asn Gly Gln Asn Gly
225                 230                 235                 240

Arg Met Glu Phe Phe Trp Thr Ile Leu Lys Pro Asn Asp Ala Ile Asn
                245                 250                 255

Phe Glu Ser Asn Gly Asn Phe Ile Ala Pro Glu Tyr Ala Tyr Lys Ile
            260                 265                 270

Val Lys Lys Gly Asp Ser Ala Ile Met Lys Ser Glu Leu Glu Tyr Gly
        275                 280                 285

Asn Cys Asn Thr Lys Cys Gln Thr Pro Met Gly Ala Ile Asn Ser Ser
    290                 295                 300

Met Pro Phe His Asn Ile His Pro Leu Thr Ile Gly Glu Cys Pro Lys
305                 310                 315                 320

Tyr Val Lys Ser Asn Arg Leu Val Leu Ala Thr Gly Leu Arg Asn Ser
                325                 330                 335

Pro Gln Arg Glu Arg Arg Arg Lys Lys Arg Gly Leu Phe Gly Ala Ile
            340                 345                 350

Ala Gly Phe Ile Glu Gly Gly Trp Gln Gly Met Val Asp Gly Trp Tyr
        355                 360                 365

Gly Tyr His His Ser Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Lys
    370                 375                 380

Glu Ser Thr Gln Lys Ala Ile Asp Gly Val Thr Asn Lys Val Asn Ser
385                 390                 395                 400

Ile Ile Asp Lys Met Asn Thr Gln Phe Glu Ala Val Gly Arg Glu Phe
                405                 410                 415

Asn Asn Leu Glu Arg Arg Ile Glu Asn Leu Asn Lys Lys Met Glu Asp
            420                 425                 430

Gly Phe Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Met
```

435 440 445

Glu Asn Glu Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu
450 455 460

Tyr Asp Lys Val Arg Leu Gln Leu Arg Asp Asn Ala Lys Glu Leu Gly
465 470 475 480

Asn Gly Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Glu Cys Met Glu
485 490 495

Ser Val Arg Asn Gly Thr Tyr Asp Tyr Pro Gln Tyr Ser Glu Glu Ala
500 505 510

Arg Leu Lys Arg Glu Glu Ile Ser Gly Val Lys Leu Glu Ser Ile Gly
515 520 525

Thr Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
530 535 540

Leu Ala Ile Met Val Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
545 550 555 560

Ser Leu Gln Cys Arg Ile Cys Ile
565

<210> 707
<211> 568
<212> PRT
<213> Influenza A virus

<400> 707

Met Glu Lys Ile Val Leu Leu Phe Ala Ile Val Ser Leu Val Lys Ser
1 5 10 15

Asp Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Gln Val
20 25 30

Asp Thr Ile Met Glu Lys Asn Val Thr Val Thr His Ala Gln Asp Ile
35 40 45

Leu Glu Lys Thr His Asn Gly Lys Leu Cys Asp Leu Asp Gly Val Lys
50 55 60

Pro Leu Ile Leu Arg Asp Cys Ser Val Ala Gly Trp Leu Leu Gly Asn
65 70 75 80

Pro Met Cys Asp Glu Phe Ile Asn Val Pro Glu Trp Ser Tyr Ile Val

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                85                  90                  95

Glu Lys Ala Asn Pro Ala Asn Asp Leu Cys Tyr Pro Gly Asp Phe Asn
            100                 105                 110

Asp Tyr Glu Glu Leu Lys His Leu Leu Ser Arg Ile Asn His Phe Glu
        115                 120                 125

Lys Ile Gln Ile Ile Pro Lys Asn Ser Trp Ser Ser His Glu Ala Ser
    130                 135                 140

Leu Gly Val Ser Ser Ala Cys Pro Tyr Gln Gly Lys Ser Ser Phe Phe
145                 150                 155                 160

Arg Asn Val Val Trp Leu Ile Lys Lys Asn Asn Ala Tyr Pro Thr Ile
                165                 170                 175

Lys Arg Ser Tyr Asn Asn Thr Asn Gln Glu Asp Leu Leu Val Leu Trp
            180                 185                 190

Gly Ile His His Pro Asn Asp Ala Ala Glu Gln Thr Arg Leu Tyr Gln
        195                 200                 205

Asn Pro Thr Thr Tyr Ile Ser Val Gly Thr Ser Thr Leu Asn Gln Arg
    210                 215                 220

Leu Val Pro Lys Ile Ala Thr Arg Ser Lys Val Asn Gly Gln Asn Gly
225                 230                 235                 240

Arg Met Glu Phe Phe Trp Thr Ile Leu Lys Pro Asn Asp Ala Ile Asn
                245                 250                 255

Phe Glu Ser Asn Gly Asn Phe Ile Ala Pro Glu Tyr Ala Tyr Lys Ile
            260                 265                 270

Val Lys Lys Gly Asp Ser Ala Ile Met Lys Ser Glu Leu Glu Tyr Gly
        275                 280                 285

Asn Cys Asn Thr Lys Cys Gln Thr Pro Met Gly Ala Ile Asn Ser Ser
    290                 295                 300

Met Pro Phe His Asn Ile His Pro Leu Thr Ile Gly Glu Cys Pro Lys
305                 310                 315                 320

Tyr Val Lys Ser Asn Arg Leu Val Leu Ala Thr Gly Leu Arg Asn Ser
                325                 330                 335
```

Pro Gln Arg Glu Arg Arg Arg Lys Lys Arg Gly Leu Phe Gly Ala Ile
340 345 350

Ala Gly Phe Ile Glu Gly Gly Trp Gln Gly Met Val Asp Gly Trp Tyr
355 360 365

Gly Tyr His His Ser Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Lys
370 375 380

Glu Ser Thr Gln Lys Ala Ile Asp Gly Val Thr Asn Lys Val Asn Ser
385 390 395 400

Ile Ile Asp Lys Met Asn Thr Gln Phe Glu Ala Val Gly Arg Glu Phe
405 410 415

Asn Asn Leu Glu Arg Arg Ile Glu Asn Leu Asn Lys Lys Met Glu Asp
420 425 430

Gly Phe Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Met
435 440 445

Glu Asn Glu Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu
450 455 460

Tyr Asp Lys Val Arg Leu Gln Leu Arg Asp Asn Ala Lys Glu Leu Gly
465 470 475 480

Asn Gly Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Glu Cys Met Glu
485 490 495

Ser Val Arg Asn Gly Thr Tyr Asp Tyr Pro Gln Tyr Ser Glu Glu Ala
500 505 510

Arg Leu Lys Arg Glu Glu Ile Ser Gly Val Lys Leu Glu Ser Ile Gly
515 520 525

Thr Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala
530 535 540

Leu Ala Ile Met Val Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly
545 550 555 560

Ser Leu Gln Cys Arg Ile Cys Ile
565

<210> 708
<211> 602
<212> PRT

<213> Homo sapiens

<400> 708

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Met His Ser Lys Val Thr Ile Ile Cys Ile Arg Phe Leu Phe Trp Phe
1               5                  10                  15

Leu Leu Leu Cys Met Leu Ile Gly Lys Ser His Thr Glu Asp Asp Ile
            20                  25                  30

Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met Asn Leu Thr Val
        35                  40                  45

Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro Tyr Ala Gln Pro
    50                  55                  60

Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser Leu Thr Lys Trp
65                  70                  75                  80

Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser Cys Cys Gln Asn
                85                  90                  95

Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu Met Trp Asn Pro
            100                 105                 110

Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn Val Trp Ile Pro
        115                 120                 125

Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp Ile Tyr Gly Gly
    130                 135                 140

Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr Asp Gly Lys Phe
145                 150                 155                 160

Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met Asn Tyr Arg Val
                165                 170                 175

Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro Glu Ala Pro Gly
            180                 185                 190

Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln Trp Val Gln Lys
        195                 200                 205

Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val Thr Leu Phe Gly
    210                 215                 220

Glu Ser Ala Gly Ala Ala Ser Val Ser Leu His Leu Leu Ser Pro Gly
225                 230                 235                 240
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Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser Gly Ser Phe Asn
                245                 250                 255

Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg Asn Arg Thr Leu
            260                 265                 270

Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn Glu Thr Glu Ile
        275                 280                 285

Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile Leu Leu Asn Glu
    290                 295                 300

Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Ser Val Asn Phe Gly Pro
305                 310                 315                 320

Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp Ile Leu Leu Glu
                325                 330                 335

Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly Val Asn Lys Asp
            340                 345                 350

Glu Gly Thr Ala Phe Leu Val Tyr Gly Ala Pro Gly Phe Ser Lys Asp
        355                 360                 365

Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu Gly Leu Lys Ile
    370                 375                 380

Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser Ile Leu Phe His
385                 390                 395                 400

Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn Tyr Arg Glu Ala
                405                 410                 415

Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys Pro Ala Leu Glu
            420                 425                 430

Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala Phe Phe Tyr Tyr
        435                 440                 445

Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu Trp Met Gly Val
    450                 455                 460

Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu Pro Leu Glu Arg
465                 470                 475                 480

Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser Arg Ser Ile Val
                485                 490                 495
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Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro Asn Glu Thr Gln
500 505 510

Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr Glu Gln Lys Tyr
515 520 525

Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr Lys Leu Arg Ala
530 535 540

Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys Val Leu Glu Met
545 550 555 560

Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys Ala Gly Phe His
565 570 575

Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln Phe Asn Asp Tyr
580 585 590

Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
595 600

<210> 709
<211> 602
<212> PRT
<213> Homo sapiens

<400> 709

Met His Ser Lys Val Thr Ile Ile Cys Ile Arg Phe Leu Phe Trp Phe
1 5 10 15

Leu Leu Leu Cys Met Leu Ile Gly Lys Ser His Thr Glu Asp Asp Ile
20 25 30

Ile Ile Ala Thr Lys Asn Gly Lys Val Arg Gly Met Asn Leu Thr Val
35 40 45

Phe Gly Gly Thr Val Thr Ala Phe Leu Gly Ile Pro Tyr Ala Gln Pro
50 55 60

Pro Leu Gly Arg Leu Arg Phe Lys Lys Pro Gln Ser Leu Thr Lys Trp
65 70 75 80

Ser Asp Ile Trp Asn Ala Thr Lys Tyr Ala Asn Ser Cys Cys Gln Asn
85 90 95

Ile Asp Gln Ser Phe Pro Gly Phe His Gly Ser Glu Met Trp Asn Pro
100 105 110

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Asn Thr Asp Leu Ser Glu Asp Cys Leu Tyr Leu Asn Val Trp Ile Pro
        115                 120                 125

Ala Pro Lys Pro Lys Asn Ala Thr Val Leu Ile Trp Ile Tyr Gly Gly
    130                 135                 140

Gly Phe Gln Thr Gly Thr Ser Ser Leu His Val Tyr Asp Gly Lys Phe
145                 150                 155                 160

Leu Ala Arg Val Glu Arg Val Ile Val Val Ser Met Asn Tyr Arg Val
                165                 170                 175

Gly Ala Leu Gly Phe Leu Ala Leu Pro Gly Asn Pro Glu Ala Pro Gly
            180                 185                 190

Asn Met Gly Leu Phe Asp Gln Gln Leu Ala Leu Gln Trp Val Gln Lys
        195                 200                 205

Asn Ile Ala Ala Phe Gly Gly Asn Pro Lys Ser Val Thr Leu Phe Gly
    210                 215                 220

Glu Ser Ala Gly Ala Ala Ser Val Ser Leu His Leu Leu Ser Pro Gly
225                 230                 235                 240

Ser His Ser Leu Phe Thr Arg Ala Ile Leu Gln Ser Gly Ser Phe Asn
                245                 250                 255

Ala Pro Trp Ala Val Thr Ser Leu Tyr Glu Ala Arg Asn Arg Thr Leu
            260                 265                 270

Asn Leu Ala Lys Leu Thr Gly Cys Ser Arg Glu Asn Glu Thr Glu Ile
        275                 280                 285

Ile Lys Cys Leu Arg Asn Lys Asp Pro Gln Glu Ile Leu Leu Asn Glu
    290                 295                 300

Ala Phe Val Val Pro Tyr Gly Thr Pro Leu Ser Val Asn Phe Gly Pro
305                 310                 315                 320

Thr Val Asp Gly Asp Phe Leu Thr Asp Met Pro Asp Ile Leu Leu Glu
                325                 330                 335

Leu Gly Gln Phe Lys Lys Thr Gln Ile Leu Val Gly Val Asn Lys Asp
            340                 345                 350

Glu Gly Thr Ala Phe Leu Val Tyr Gly Ala Pro Gly Phe Ser Lys Asp
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        355                 360                 365

Asn Asn Ser Ile Ile Thr Arg Lys Glu Phe Gln Glu Gly Leu Lys Ile
    370                 375                 380

Phe Phe Pro Gly Val Ser Glu Phe Gly Lys Glu Ser Ile Leu Phe His
385                 390                 395                 400

Tyr Thr Asp Trp Val Asp Asp Gln Arg Pro Glu Asn Tyr Arg Glu Ala
                405                 410                 415

Leu Gly Asp Val Val Gly Asp Tyr Asn Phe Ile Cys Pro Ala Leu Glu
            420                 425                 430

Phe Thr Lys Lys Phe Ser Glu Trp Gly Asn Asn Ala Phe Phe Tyr Tyr
        435                 440                 445

Phe Glu His Arg Ser Ser Lys Leu Pro Trp Pro Glu Trp Met Gly Val
    450                 455                 460

Met His Gly Tyr Glu Ile Glu Phe Val Phe Gly Leu Pro Leu Glu Arg
465                 470                 475                 480

Arg Asp Asn Tyr Thr Lys Ala Glu Glu Ile Leu Ser Arg Ser Ile Val
                485                 490                 495

Lys Arg Trp Ala Asn Phe Ala Lys Tyr Gly Asn Pro Asn Glu Thr Gln
            500                 505                 510

Asn Asn Ser Thr Ser Trp Pro Val Phe Lys Ser Thr Glu Gln Lys Tyr
        515                 520                 525

Leu Thr Leu Asn Thr Glu Ser Thr Arg Ile Met Thr Lys Leu Arg Ala
    530                 535                 540

Gln Gln Cys Arg Phe Trp Thr Ser Phe Phe Pro Lys Val Leu Glu Met
545                 550                 555                 560

Thr Gly Asn Ile Asp Glu Ala Glu Trp Glu Trp Lys Ala Gly Phe His
                565                 570                 575

Arg Trp Asn Asn Tyr Met Met Asp Trp Lys Asn Gln Phe Asn Asp Tyr
            580                 585                 590

Thr Ser Lys Lys Glu Ser Cys Val Gly Leu
        595                 600
```

<210> 710
<211> 52
<212> PRT
<213> Homo sapiens

<400> 710

Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 711
<211> 52
<212> PRT
<213> Homo sapiens

<400> 711

Tyr Arg Gln Ser Met Asn Asn Phe Gln Gly Leu Arg Ser Phe Gly Cys
1 5 10 15

Arg Phe Gly Thr Cys Thr Val Gln Lys Leu Ala His Gln Ile Tyr Gln
20 25 30

Phe Thr Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser
35 40 45

Pro Gln Gly Tyr
50

<210> 712
<211> 36
<212> PRT
<213> Homo sapiens

<400> 712

Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 713
<211> 36
<212> PRT
<213> Homo sapiens

<400> 713

Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 714
<211> 165
<212> PRT
<213> Homo sapiens

<400> 714

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 715
<211> 165
<212> PRT
<213> Homo sapiens

<400> 715

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 716
<211> 165
<212> PRT

<213> Homo sapiens

<400> 716

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
35 40 45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
50 55 60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65 70 75 80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 717
<211> 165
<212> PRT
<213> Homo sapiens

<400> 717

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1 5 10 15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
20 25 30

```
Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210>  718
<211>  165
<212>  PRT
<213>  Homo sapiens

<400>  718

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80
```

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
85 90 95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
100 105 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
115 120 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
130 135 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145 150 155 160

Leu Arg Ser Lys Glu
165

<210> 719
<211> 46
<212> DNA
<213> Homo sapiens

<400> 719
caagctgcct taggcttaca ctcccaaggt accttcacct ccgact 46

<210> 720
<211> 59
<212> DNA
<213> Homo sapiens

<400> 720
gcgcgcgcct aaggttacta ggcgatgtta tttctgtttc tcttggtgtt catcaacca 59

<210> 721
<211> 46
<212> DNA
<213> Homo sapiens

<400> 721
caagctgcct taggcttaca ctcccaaggt accttcacct ccgact 46

<210> 722
<211> 59
<212> DNA
<213> Homo sapiens

<400> 722
gcgcgcgcct aaggttacta ggcgatgtta tttctgtttc tcttggtgtt catcaacca 59

<210> 723
<211> 33
<212> DNA

<213> Homo sapiens

<400> 723
aggagcgtcg acaaaagatg cagctgcgcc ccg 33

<210> 724
<211> 51
<212> DNA
<213> Homo sapiens

<400> 724
cgcgcatcga tgagcaacct cactcttgtg tgcatcgcca cagttcagat g 51

<210> 725
<211> 32
<212> DNA
<213> Homo sapiens

<400> 725
aagctgcctt aggcttatgc agctgcgccc cg 32

<210> 726
<211> 28
<212> DNA
<213> Homo sapiens

<400> 726
ttggcgcgcc tcagccacag ttcagatg 28

<210> 727
<211> 41
<212> DNA
<213> Homo sapiens

<400> 727
gcccccgccc gcggcatcaa acccgaggct cccggcgaag a 41

<210> 728
<211> 63
<212> DNA
<213> Homo sapiens

<400> 728
caagctgcct taggcttagg ctccagcttc ctgagccctg aacaccagag agtccagcag 60

aga 63

<210> 729
<211> 41
<212> DNA
<213> Homo sapiens

<400> 729
cgcgcgccta aggtcattat cggggctgca gcttggctgg t 41

<210> 730

<211> 63
<212> DNA
<213> Homo sapiens

<400> 730
caagctgcct taggcttagg ctccagcttc ctgagccctg aacaccagag agtccagcag 60

aga 63

<210> 731
<211> 41
<212> DNA
<213> Homo sapiens

<400> 731
cgcgcgccta aggtcattat cggggctgca gcttggctgg t 41

<210> 732
<211> 108
<212> DNA
<213> Homo sapiens

<400> 732
taccccatca aacccgaggc tcccggcgaa gacgcctcgc cggaggagct gaaccgctac 60

tacgcctccc tgcgccacta cctcaacctg gtcacccggc agcggtat 108

<210> 733
<211> 102
<212> DNA
<213> Homo sapiens

<400> 733
atcaaacccg aggctcccgg cgaagacgcc tcgccggagg agctgaaccg ctactacgcc 60

tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 734
<211> 102
<212> DNA
<213> Homo sapiens

<400> 734
atcaaacccg aggctcccgg cgaagacgcc tcgccggagg agctgaaccg ctactacgcc 60

tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 735
<211> 102
<212> DNA
<213> Homo sapiens

<400> 735
atcaaacccg aggctcccgg cgaagacgcc tcgccggagg agctgaaccg ctactacgcc 60

tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 736
<211> 102
<212> DNA
<213> Homo sapiens

<400> 736
atcaaacccg aggctcccgg cgaagacgcc tcgccggagg agctgaaccg ctactacgcc 60

tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 737
<211> 102
<212> DNA
<213> Homo sapiens

<400> 737
atcaaacccg aggctcccgg cgaagacgcc tcgccggagg agctgaaccg ctactacgcc 60

tccctgcgcc actacctcaa cctggtcacc cggcagcggt at 102

<210> 738
<211> 78
<212> DNA
<213> Homo sapiens

<400> 738
gcacaccaga tctaccagtt cacagataag gacaaggaca acgtcgcccc caggagcaag 60

atcagccccc agggctac 78

<210> 739
<211> 111
<212> DNA
<213> Homo sapiens

<400> 739
cattcacagg gcacattcac cagtgactac agcaagtatc tggactccag gcgtgcccaa 60

gattttgtgc agtggttgat gaataccaag aggaacagga ataacattgc c 111

<210> 740
<211> 111
<212> DNA
<213> Homo sapiens

<400> 740
cattcacagg gcacattcac cagtgactac agcaagtatc tggactccag gcgtgcccaa 60

gattttgtgc agtggttgat gaataccaag aggaacagga ataacattgc c 111

<210> 741
<211> 84
<212> DNA
<213> Homo sapiens

<400> 741
ggctccagct tcctgagccc tgaacaccag agagtccagc agagaaagga gtcgaagaag 60

ccaccagcca agctgcagcc ccga 84

<210> 742
<211> 675
<212> DNA
<213> Homo sapiens

<400> 742
atgcctggga gccctcggcc cgcgccaagc tgggtgctgt tgctgcggct gctggcgttg 60

ctgcggcccc cggggctggg tgaggcatgc agctgcgccc cggcgcaccc tcagcagcac 120

atctgccact cggcacttgt gattcgggcc aaaatctcca gtgagaaggt agttccggcc 180

agtgcagacc ctgctgacac tgaaaaaatg ctccggtatg aaatcaaaca gataaagatg 240

ttcaaagggt ttgagaaagt caaggatgtt cagtatatct atacgccttt tgactcttcc 300

ctctgtggtg tgaaactaga agccaacagc cagaagcagt atctcttgac tggtcaggtc 360

ctcagtgatg gaaaagtctt catccatctg tgcaactaca tcgagccctg ggaggacctg 420

tccttggtgc agagggaaag tctgaatcat cactaccatc tgaactgtgg ctgccaaatc 480

accacctgct acacagtacc ctgtaccatc tcggccccta acgagtgcct ctggacagac 540

tggctgttgg aacgaaagct ctatggttac caggctcagc attatgtctg tatgaagcat 600

gttgacggca cctgcagctg gtaccggggc cacctgcctc tcaggaagga gtttgttgac 660

atcgttcagc cctag 675

<210> 743
<211> 675
<212> DNA
<213> Homo sapiens

<400> 743
atgcctggga gccctcggcc cgcgccaagc tgggtgctgt tgctgcggct gctggcgttg 60

ctgcggcccc cggggctggg tgaggcatgc agctgcgccc cggcgcaccc tcagcagcac 120

atctgccact cggcacttgt gattcgggcc aaaatctcca gtgagaaggt agttccggcc 180

agtgcagacc ctgctgacac tgaaaaaatg ctccggtatg aaatcaaaca gataaagatg 240

ttcaaagggt ttgagaaagt caaggatgtt cagtatatct atacgccttt tgactcttcc 300

ctctgtggtg tgaaactaga agccaacagc cagaagcagt atctcttgac tggtcaggtc 360

ctcagtgatg gaaaagtctt catccatctg tgcaactaca tcgagccctg ggaggacctg 420

tccttggtgc agagggaaag tctgaatcat cactaccatc tgaactgtgg ctgccaaatc 480

accacctgct acacagtacc ctgtaccatc tcggccccta acgagtgcct ctggacagac 540

tggctgttgg aacgaaagct ctatggttac caggctcagc attatgtctg tatgaagcat 600

gttgacggca cctgcagctg gtaccggggc cacctgcctc tcaggaagga gtttgttgac 660

atcgttcagc cctag 675

<210> 744
<211> 645
<212> PRT
<213> Homo sapiens

<400> 744

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
180 185 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
195 200 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
210 215 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
245 250 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
260 265 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
275 280 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val

```
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
    610                 615                 620

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
625                 630                 635                 640

Thr Arg Gln Arg Tyr
                645


<210>  745
<211>  643
<212>  PRT
<213>  Homo sapiens

<400>  745

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
```

```
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285
```

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
290 295 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305 310 315 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

```
Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
    610                 615                 620

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625                 630                 635                 640

Gln Arg Tyr
```

<210> 746
<211> 643
<212> PRT
<213> Homo sapiens

<400> 746

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Ile Lys Pro Glu Ala Pro Gly Glu
            20                  25                  30

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
        35                  40                  45

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys Ser Glu
    50                  55                  60

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
65                  70                  75                  80

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
                85                  90                  95

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
            100                 105                 110
```

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
115 120 125

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
130 135 140

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
145 150 155 160

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
165 170 175

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe
180 185 190

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
195 200 205

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
210 215 220

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
225 230 235 240

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
245 250 255

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
260 265 270

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
275 280 285

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
290 295 300

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
305 310 315 320

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
325 330 335

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
340 345 350

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
355 360 365

```
Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
    370                 375                 380

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
385                 390                 395                 400

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
                405                 410                 415

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
            420                 425                 430

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
        435                 440                 445

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
    450                 455                 460

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
465                 470                 475                 480

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
                485                 490                 495

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
            500                 505                 510

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
        515                 520                 525

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
    530                 535                 540

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
545                 550                 555                 560

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
                565                 570                 575

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
            580                 585                 590

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
        595                 600                 605

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
```

610 615 620

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
625 630 635 640

Leu Gly Leu

<210> 747
<211> 643
<212> PRT
<213> Homo sapiens

<400> 747

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Ile Lys Pro Glu Ala Pro Gly Glu
20 25 30

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
35 40 45

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys Ser Glu
50 55 60

Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu
65 70 75 80

Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp
85 90 95

His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val
100 105 110

Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe
115 120 125

Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu
130 135 140

Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
145 150 155 160

Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro
165 170 175

Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe

180 185 190

Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr
195 200 205

Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr
210 215 220

Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu
225 230 235 240

Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
245 250 255

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
260 265 270

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
275 280 285

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
290 295 300

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
305 310 315 320

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
325 330 335

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
340 345 350

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
355 360 365

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
370 375 380

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
385 390 395 400

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
405 410 415

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
420 425 430

```
Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
        435                 440                 445

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
    450                 455                 460

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
465                 470                 475                 480

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
                485                 490                 495

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
            500                 505                 510

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
        515                 520                 525

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
    530                 535                 540

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
545                 550                 555                 560

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
                565                 570                 575

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
            580                 585                 590

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
        595                 600                 605

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
    610                 615                 620

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
625                 630                 635                 640

Leu Gly Leu
```

<210> 748
<211> 677
<212> PRT
<213> Homo sapiens

<400> 748

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ile Lys Pro Glu Ala Pro Gly Glu
            20                  25                  30

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
        35                  40                  45

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Ile Lys Pro Glu Ala Pro
    50                  55                  60

Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu
65                  70                  75                  80

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr Asp Ala His Lys
                85                  90                  95

Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys
            100                 105                 110

Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe
        115                 120                 125

Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr
    130                 135                 140

Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr
145                 150                 155                 160

Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr
                165                 170                 175

Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu
            180                 185                 190

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val
        195                 200                 205

Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu
    210                 215                 220

Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr
225                 230                 235                 240

Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala
                245                 250                 255
```

```
Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro
            260                 265                 270

Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln
        275                 280                 285

Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys
    290                 295                 300

Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe
305                 310                 315                 320

Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu
                325                 330                 335

Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu
            340                 345                 350

Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys
        355                 360                 365

Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu
    370                 375                 380

Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp
385                 390                 395                 400

Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp
                405                 410                 415

Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp
            420                 425                 430

Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr
        435                 440                 445

Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys
    450                 455                 460

Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile
465                 470                 475                 480

Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln
                485                 490                 495

Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr
            500                 505                 510
```

```
Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys
        515                 520                 525

Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr
    530                 535                 540

Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro
545                 550                 555                 560

Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg
                565                 570                 575

Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys
            580                 585                 590

Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu
        595                 600                 605

Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu
    610                 615                 620

Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met
625                 630                 635                 640

Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys
                645                 650                 655

Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln
            660                 665                 670

Ala Ala Leu Gly Leu
        675


<210>  749
<211>  677
<212>  PRT
<213>  Homo sapiens

<400>  749

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45
```

```
Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
```

```
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540
```

```
Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
    610                 615                 620

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
625                 630                 635                 640

Gln Arg Tyr Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu
                645                 650                 655

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
            660                 665                 670

Thr Arg Gln Arg Tyr
        675


<210>  750
<211>  635
<212>  PRT
<213>  Homo sapiens

<400>  750

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Ala His Gln Ile Tyr Gln Phe Thr
            20                  25                  30

Asp Lys Asp Lys Asp Asn Val Ala Pro Arg Ser Lys Ile Ser Pro Gln
        35                  40                  45

Gly Tyr Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu
    50                  55                  60

Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr
65                  70                  75                  80
```

```
Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val
                85                  90                  95

Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys
            100                 105                 110

Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala
        115                 120                 125

Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln
    130                 135                 140

Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
145                 150                 155                 160

Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala
                165                 170                 175

Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile
            180                 185                 190

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala
        195                 200                 205

Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys
    210                 215                 220

Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys
225                 230                 235                 240

Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe
                245                 250                 255

Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg
            260                 265                 270

Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu
        275                 280                 285

Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala
    290                 295                 300

Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser
305                 310                 315                 320

Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys
                325                 330                 335
```

```
Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu
            340                 345                 350

Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn
        355                 360                 365

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr
    370                 375                 380

Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala
385                 390                 395                 400

Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro
                405                 410                 415

His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu
            420                 425                 430

Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu
        435                 440                 445

Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys
    450                 455                 460

Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu
465                 470                 475                 480

Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met
                485                 490                 495

Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val
            500                 505                 510

Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr
        515                 520                 525

Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp
    530                 535                 540

Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His
545                 550                 555                 560

Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln
                565                 570                 575

Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu
            580                 585                 590
```

Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys
595 600 605

Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys
610 615 620

Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 751
<211> 646
<212> PRT
<213> Homo sapiens

<400> 751

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
20 25 30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
35 40 45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
50 55 60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
100 105 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
130 135 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145 150 155 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

```
Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
```

```
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
            580                 585                 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
        595                 600                 605

Leu His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp
    610                 615                 620

Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg
625                 630                 635                 640

Asn Arg Asn Asn Ile Ala
                645


<210>  752
<211>  646
<212>  PRT
<213>  Homo sapiens
```

<400> 752

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg His Ser Gln Gly Thr Phe Thr Ser
20 25 30

Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln
35 40 45

Trp Leu Met Asn Thr Lys Arg Asn Arg Asn Asn Ile Ala Asp Ala His
50 55 60

Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe
65 70 75 80

Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro
85 90 95

Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys
100 105 110

Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His
115 120 125

Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr
130 135 140

Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn
145 150 155 160

Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu
165 170 175

Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu
180 185 190

Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro
195 200 205

Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala
210 215 220

Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu
225 230 235 240

```
Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys
                245                 250                 255

Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe
            260                 265                 270

Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu
        275                 280                 285

Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr
    290                 295                 300

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp
305                 310                 315                 320

Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu
                325                 330                 335

Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala
            340                 345                 350

Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala
        355                 360                 365

Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys
    370                 375                 380

Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro
385                 390                 395                 400

Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr
                405                 410                 415

Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala
            420                 425                 430

Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu
        435                 440                 445

Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe
    450                 455                 460

Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser
465                 470                 475                 480

Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser
                485                 490                 495
```

```
Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp
            500                 505                 510

Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr
        515                 520                 525

Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn
    530                 535                 540

Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro
545                 550                 555                 560

Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr
                565                 570                 575

Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu
            580                 585                 590

Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val
        595                 600                 605

Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp
    610                 615                 620

Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser
625                 630                 635                 640

Gln Ala Ala Leu Gly Leu
                645


<210>  753
<211>  636
<212>  PRT
<213>  Homo sapiens

<400>  753

Met Arg Pro Thr Trp Ala Trp Trp Leu Phe Leu Val Leu Leu Leu Ala
1               5                   10                  15

Leu Trp Ala Pro Ala Arg Gly Gly Ser Ser Phe Leu Ser Pro Glu His
            20                  25                  30

Gln Arg Val Gln Gln Arg Lys Glu Ser Lys Lys Pro Pro Ala Lys Leu
        35                  40                  45

Gln Pro Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp
    50                  55                  60
```

```
Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln
65                  70                  75                  80

Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu
                85                  90                  95

Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn
            100                 105                 110

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val
        115                 120                 125

Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys
    130                 135                 140

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
145                 150                 155                 160

Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr
                165                 170                 175

Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu
            180                 185                 190

Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe
        195                 200                 205

Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp
    210                 215                 220

Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly
225                 230                 235                 240

Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys
                245                 250                 255

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln
            260                 265                 270

Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp
        275                 280                 285

Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys
    290                 295                 300

Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp
305                 310                 315                 320
```

Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu
325 330 335

Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp
340 345 350

Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys
355 360 365

Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu
370 375 380

Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu
385 390 395 400

Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp
405 410 415

Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val
420 425 430

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
435 440 445

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
450 455 460

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
465 470 475 480

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
485 490 495

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
500 505 510

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
515 520 525

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
530 535 540

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
545 550 555 560

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys

565 570 575

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
580 585 590

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
595 600 605

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
610 615 620

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
625 630 635

<210> 754
<211> 804
<212> PRT
<213> Homo sapiens

<400> 754

Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1 5 10 15

Tyr Ser Arg Ser Leu Asp Lys Arg Cys Ser Cys Ala Pro Ala His Pro
20 25 30

Gln Gln His Ile Cys His Ser Ala Leu Val Ile Arg Ala Lys Ile Ser
35 40 45

Ser Glu Lys Val Val Pro Ala Ser Ala Asp Pro Ala Asp Thr Glu Lys
50 55 60

Met Leu Arg Tyr Glu Ile Lys Gln Ile Lys Met Phe Lys Gly Phe Glu
65 70 75 80

Lys Val Lys Asp Val Gln Tyr Ile Tyr Thr Pro Phe Asp Ser Ser Leu
85 90 95

Cys Gly Val Lys Leu Glu Ala Asn Ser Gln Lys Gln Tyr Leu Leu Thr
100 105 110

Gly Gln Val Leu Ser Asp Gly Lys Val Phe Ile His Leu Cys Asn Tyr
115 120 125

Ile Glu Pro Trp Glu Asp Leu Ser Leu Val Gln Arg Glu Ser Leu Asn
130 135 140

His His Tyr His Leu Asn Cys Gly Cys Gln Ile Thr Thr Cys Tyr Thr

```
145                 150                 155                 160

Val Pro Cys Thr Ile Ser Ala Pro Asn Glu Cys Leu Trp Thr Asp Trp
                165                 170                 175

Leu Leu Glu Arg Lys Leu Tyr Gly Tyr Gln Ala Gln His Tyr Val Cys
            180                 185                 190

Met Lys His Val Asp Gly Thr Cys Ser Trp Tyr Arg Gly His Leu Pro
        195                 200                 205

Leu Arg Lys Glu Phe Val Asp Ile Val Gln Pro Asp Ala His Lys Ser
    210                 215                 220

Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala
225                 230                 235                 240

Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu
                245                 250                 255

Asp His Val Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys
            260                 265                 270

Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu
        275                 280                 285

Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly
    290                 295                 300

Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys
305                 310                 315                 320

Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg
                325                 330                 335

Pro Glu Val Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr
            340                 345                 350

Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe
        355                 360                 365

Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe
    370                 375                 380

Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys
385                 390                 395                 400
```

Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg
405 410 415

Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
420 425 430

Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala
435 440 445

Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys
450 455 460

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala
465 470 475 480

Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu
485 490 495

Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val
500 505 510

Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe
515 520 525

Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
530 535 540

Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr
545 550 555 560

Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu
565 570 575

Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val
580 585 590

Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys
595 600 605

Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn
610 615 620

Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro
625 630 635 640

Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys
645 650 655

```
Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu
            660                 665                 670

Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val
        675                 680                 685

Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg
    690                 695                 700

Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu
705                 710                 715                 720

Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser
                725                 730                 735

Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val
            740                 745                 750

Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp
        755                 760                 765

Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu
    770                 775                 780

Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala
785                 790                 795                 800

Ala Leu Gly Leu
```

<210> 755
<211> 804
<212> PRT
<213> Homo sapiens

<400> 755

```
Met Lys Trp Val Ser Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Ser Leu Asp Lys Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60
```

```
Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320
```

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
325 330 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
355 360 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
370 375 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385 390 395 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
405 410 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala

565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu Cys Ser Cys Ala Pro Ala His Pro Gln Gln His Ile Cys His Ser
610 615 620

Ala Leu Val Ile Arg Ala Lys Ile Ser Ser Glu Lys Val Val Pro Ala
625 630 635 640

Ser Ala Asp Pro Ala Asp Thr Glu Lys Met Leu Arg Tyr Glu Ile Lys
645 650 655

Gln Ile Lys Met Phe Lys Gly Phe Glu Lys Val Lys Asp Val Gln Tyr
660 665 670

Ile Tyr Thr Pro Phe Asp Ser Ser Leu Cys Gly Val Lys Leu Glu Ala
675 680 685

Asn Ser Gln Lys Gln Tyr Leu Leu Thr Gly Gln Val Leu Ser Asp Gly
690 695 700

Lys Val Phe Ile His Leu Cys Asn Tyr Ile Glu Pro Trp Glu Asp Leu
705 710 715 720

Ser Leu Val Gln Arg Glu Ser Leu Asn His His Tyr His Leu Asn Cys
725 730 735

Gly Cys Gln Ile Thr Thr Cys Tyr Thr Val Pro Cys Thr Ile Ser Ala
740 745 750

Pro Asn Glu Cys Leu Trp Thr Asp Trp Leu Leu Glu Arg Lys Leu Tyr
755 760 765

Gly Tyr Gln Ala Gln His Tyr Val Cys Met Lys His Val Asp Gly Thr
770 775 780

Cys Ser Trp Tyr Arg Gly His Leu Pro Leu Arg Lys Glu Phe Val Asp
785 790 795 800

Ile Val Gln Pro

<210> 756
<211> 36
<212> PRT
<213> Homo sapiens

<400> 756

Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 757
<211> 34
<212> PRT
<213> Homo sapiens

<400> 757

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

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 758
<211> 34
<212> PRT
<213> Homo sapiens

<400> 758

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

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 759
<211> 34
<212> PRT
<213> Homo sapiens

<400> 759

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

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 760
<211> 34
<212> PRT
<213> Homo sapiens

<400> 760

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

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 761
<211> 34
<212> PRT
<213> Homo sapiens

<400> 761

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

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 762
<211> 26
<212> PRT
<213> Homo sapiens

<400> 762

Ala His Gln Ile Tyr Gln Phe Thr Asp Lys Asp Lys Asp Asn Val Ala
1 5 10 15

Pro Arg Ser Lys Ile Ser Pro Gln Gly Tyr

20 25

<210> 763
<211> 37
<212> PRT
<213> Homo sapiens

<400> 763

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile Ala
35

<210> 764
<211> 37
<212> PRT
<213> Homo sapiens

<400> 764

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1 5 10 15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn
20 25 30

Arg Asn Asn Ile Ala
35

<210> 765
<211> 28
<212> PRT
<213> Homo sapiens

<400> 765

Gly Ser Ser Phe Leu Ser Pro Glu His Gln Arg Val Gln Gln Arg Lys
1 5 10 15

Glu Ser Lys Lys Pro Pro Ala Lys Leu Gln Pro Arg
20 25

<210> 766
<211> 224
<212> PRT
<213> Homo sapiens

<400> 766

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Met Pro Gly Ser Pro Arg Pro Ala Pro Ser Trp Val Leu Leu Leu Arg
1               5                   10                  15

Leu Leu Ala Leu Leu Arg Pro Pro Gly Leu Gly Glu Ala Cys Ser Cys
            20                  25                  30

Ala Pro Ala His Pro Gln Gln His Ile Cys His Ser Ala Leu Val Ile
        35                  40                  45

Arg Ala Lys Ile Ser Ser Glu Lys Val Val Pro Ala Ser Ala Asp Pro
    50                  55                  60

Ala Asp Thr Glu Lys Met Leu Arg Tyr Glu Ile Lys Gln Ile Lys Met
65                  70                  75                  80

Phe Lys Gly Phe Glu Lys Val Lys Asp Val Gln Tyr Ile Tyr Thr Pro
                85                  90                  95

Phe Asp Ser Ser Leu Cys Gly Val Lys Leu Glu Ala Asn Ser Gln Lys
            100                 105                 110

Gln Tyr Leu Leu Thr Gly Gln Val Leu Ser Asp Gly Lys Val Phe Ile
        115                 120                 125

His Leu Cys Asn Tyr Ile Glu Pro Trp Glu Asp Leu Ser Leu Val Gln
    130                 135                 140

Arg Glu Ser Leu Asn His His Tyr His Leu Asn Cys Gly Cys Gln Ile
145                 150                 155                 160

Thr Thr Cys Tyr Thr Val Pro Cys Thr Ile Ser Ala Pro Asn Glu Cys
                165                 170                 175

Leu Trp Thr Asp Trp Leu Leu Glu Arg Lys Leu Tyr Gly Tyr Gln Ala
            180                 185                 190

Gln His Tyr Val Cys Met Lys His Val Asp Gly Thr Cys Ser Trp Tyr
        195                 200                 205

Arg Gly His Leu Pro Leu Arg Lys Glu Phe Val Asp Ile Val Gln Pro
    210                 215                 220
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<210> 767
<211> 224
<212> PRT
<213> Homo sapiens

<400> 767

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Met Pro Gly Ser Pro Arg Pro Ala Pro Ser Trp Val Leu Leu Leu Arg
1               5                   10                  15

Leu Leu Ala Leu Leu Arg Pro Pro Gly Leu Gly Glu Ala Cys Ser Cys
            20                  25                  30

Ala Pro Ala His Pro Gln Gln His Ile Cys His Ser Ala Leu Val Ile
        35                  40                  45

Arg Ala Lys Ile Ser Ser Glu Lys Val Val Pro Ala Ser Ala Asp Pro
    50                  55                  60

Ala Asp Thr Glu Lys Met Leu Arg Tyr Glu Ile Lys Gln Ile Lys Met
65                  70                  75                  80

Phe Lys Gly Phe Glu Lys Val Lys Asp Val Gln Tyr Ile Tyr Thr Pro
                85                  90                  95

Phe Asp Ser Ser Leu Cys Gly Val Lys Leu Glu Ala Asn Ser Gln Lys
            100                 105                 110

Gln Tyr Leu Leu Thr Gly Gln Val Leu Ser Asp Gly Lys Val Phe Ile
        115                 120                 125

His Leu Cys Asn Tyr Ile Glu Pro Trp Glu Asp Leu Ser Leu Val Gln
    130                 135                 140

Arg Glu Ser Leu Asn His His Tyr His Leu Asn Cys Gly Cys Gln Ile
145                 150                 155                 160

Thr Thr Cys Tyr Thr Val Pro Cys Thr Ile Ser Ala Pro Asn Glu Cys
                165                 170                 175

Leu Trp Thr Asp Trp Leu Leu Glu Arg Lys Leu Tyr Gly Tyr Gln Ala
            180                 185                 190

Gln His Tyr Val Cys Met Lys His Val Asp Gly Thr Cys Ser Trp Tyr
        195                 200                 205

Arg Gly His Leu Pro Leu Arg Lys Glu Phe Val Asp Ile Val Gln Pro
    210                 215                 220


<210>  768
<211>  47
<212>  DNA
<213>  Homo sapiens

<400>  768
ccgccgctcg aggggtgtgt ttcgtcgaat caaacccgag gctcccg                    47
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<210> 769
<211> 55
<212> DNA
<213> Homo sapiens

<400> 769
agtcccatcg atgagcaacc tcactcttgt gtgcatcata ccgctgccgg gtgac 55

<210> 770
<211> 37
<212> DNA
<213> Homo sapiens

<400> 770
aggagcgtcg acaaaagaat caaacccgag gctcccg 37

<210> 771
<211> 58
<212> DNA
<213> Homo sapiens

<400> 771
cgcgcatcga tgagcaacct cactcttgtg tgcatcatac cgctgccggg tgaccagg 58

<210> 772
<211> 23
<212> DNA
<213> Homo sapiens

<400> 772
attccaggag cgtcgacaaa aga 23

<210> 773
<211> 36
<212> DNA
<213> Homo sapiens

<400> 773
cgcgcatcga tgagcaacct cactcttgtg tgcatc 36

<210> 774
<211> 23
<212> DNA
<213> Homo sapiens

<400> 774
caagtcaagc tgccttaggc tta 23

<210> 775
<211> 26
<212> DNA
<213> Homo sapiens

<400> 775
cagtttaaac ggccggccgg cgcgcc 26

<210> 776
<211> 39
<212> DNA
<213> Homo sapiens

<400> 776
aggagcgtcg acaaaagagc acaccagatc taccagttc 39

<210> 777
<211> 55
<212> DNA
<213> Homo sapiens

<400> 777
cgcgcatcga tgagcaacct cactcttgtg tgcatcgtag ccctgggggc tgatc 55

<210> 778
<211> 60
<212> DNA
<213> Homo sapiens

<400> 778
gcccccgccc gcggcggctc cagcttcctg agccctgaac accagagagt ccagcagaga 60

<210> 779
<211> 56
<212> DNA
<213> Homo sapiens

<400> 779
ctttaaatcg atgagcaacc tcactcttgt gtgcatctcg gggctgcagc ttggct 56

<210> 780
<211> 36
<212> PRT
<213> Homo sapiens

<400> 780

Tyr Pro Ile Lys Pro Glu Ala Pro Arg Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 781
<211> 38
<212> PRT
<213> Homo sapiens

<400> 781

Cys Ser Cys Ser Ser Leu Met Asp Lys Glu Cys Val Tyr Phe Cys His
1 5 10 15

Leu Asp Ile Ile Trp Val Asn Thr Pro Glu His Val Val Pro Tyr Gly
20 25 30

Leu Gly Ser Pro Arg Ser
35

<210> 782
<211> 21
<212> PRT
<213> Homo sapiens

<400> 782

Cys Ser Cys Ser Ser Leu Met Asp Lys Glu Cys Val Tyr Phe Cys His
1 5 10 15

Leu Asp Ile Ile Trp
20

<210> 783
<211> 24
<212> PRT
<213> Homo sapiens

<400> 783

Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr Lys Ser Gln Arg Arg Lys
1 5 10 15

Gly Ser Thr Phe Glu Glu His Lys
20

<210> 784
<211> 110
<212> PRT
<213> Homo sapiens

<400> 784

Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
20 25 30

Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
35 40 45

Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu

```
    50                  55                  60

Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
65                  70                  75                  80

Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr
                85                  90                  95

Lys Ser Gln Arg Arg Lys Gly Ser Thr Phe Glu Glu His Lys
            100                 105                 110
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