Robo1-Fc fusion protein and use thereof for treating tumours

The present invention relates to a recombinant protein Robo1-Fc and to the use thereof for treating diseases in which a Slit protein is overexpressed, in particular cancer. It also relates to a composition comprising such a recombinant protein. Another aspect of the invention consists of the use of a Robo1-Fc molecule as a diagnostic tool for detecting the overexpression of a molecule of the Slit family in a patient.

Slit ligands were first of all described for their role in repelling axonal growth in neuronal development. Since then, the Robo/Slit regulatory pathway has also been described in tumour angiogenesis. Specifically, the Robo4/Slit2 pathway has been described for inhibiting the response of endothelial cells to VEGF (Jones C.A. *et al. Nat. Med* **14**, 448–453 (2008)). Regulation by the Robo/Slit pathway makes it possible to channel the excessive proliferation of endothelial non-mature neovessels or buds (non-productive angiogenesis) and to mature these vessels. The expression of Slit2 at the transcriptional level has been demonstrated in several human cancer lines, in particular HCT116 derived from colon carcinoma, Skov-3 derived from ovarian carcinoma, HeLa derived from cervical cancer, MDA-MB-435 derived from melanoma, Hec-1A derived from uterine cancer and, finally, 769-P derived from renal carcinoma (Stella MC *et al.*, Mol Biol Cell. 2009 Vol. 20, Issue 2, 642-657). Overexpression of the Slit2 protein has also been demonstrated on human tissues derived from carcinomas: oral carcinoma (Wang *et al.* 2008, Cancer Sci. 2008 Mar; 99(3): 510-7), prostate carcinoma (Latil et al. 2003 Int J Cancer. 2003 Jan 20; 103(3): 306-15), colon carcinoma (Wang *et al.* 2003, Cancer Cell, Volume 4, Issue 1, July 2003, Pages 19-29), and liver carcinoma (Avci *et al*, 2008, BMC cancer, **8**: 392). More recently, overexpression of the Slit2 protein has been shown on samples of endometriosis (Shen *et al*, 2009, *AJP* 175 (2): 479).

The Robo1 protein exists as two isoforms a and b. The extracellular domain of the Robo1 protein isoform b (NP_598334) comprises 5 immunoglobulin domains: Ig1, Ig2, Ig3, Ig4 and Ig5. The Robo protein interacts with the Slit ligands at the level of the Ig1 and Ig2 domains. Liu *et al.* (2004, Mol. Cell Neurosci, 26: 232-240) have demonstrated the importance of the Ig2 domain in the interaction with Slit and in the activity of Robo (chemorepulsion).

The use of antibodies specific for the Robo1 and the Slit2 proteins has been described in application WO2003/075860. These antibodies make it possible to inhibit tumour angiogenesis.

However, it would be advantageous to propose an alternative approach for treating cancer, in particular a molecule capable of inhibiting the Slit2 signalling pathway.

The inventors have developed a strategy of soluble chimeric Robo1 receptors capable of binding Slit ligands and consequently, of inhibiting the intracellular signalling of the Robo/Slit pathway. Surprisingly, the Robo1-Fc molecules according to the invention have an anti-angiogenesis effect by preventing the formation of mature vessels and not by inhibiting the proliferation of endothelial cells.

DETAILED DESCRIPTION OF THE INVENTION

A subject of the present invention is a Robo-Fc recombinant protein comprising the extracellular domain of the Robo1 protein, isoform b or a part of this domain, a junction region (linker) and an immunoglobulin Fc domain.

In one particular embodiment, the extracellular domain of the Robo1 protein, isoform b consists of the Ig1 and Ig2 domains. These domains correspond to the peptide of SEQ ID NO.2 encoded by the nucleotide sequence SEQ ID NO.1, or a sequence having at least 80%, 85%, 90%, 95% or 99% identity with the sequence SEQ ID NO.2.

The fusion protein also comprises a junction region, also called "linker". In the context of the present invention, the linker makes it possible to give the recombinant protein stability, in particular by limiting *in vivo* cleavage. Linkers that can be used in a Robo1-Fc molecule are, for example, GluArgProSerPheVal and GlyGlyGlyGlySer. Those skilled in the art have sufficient knowledge to select a linker suitable for this use.

The Fc domain of the Robo1-Fc recombinant molecules according to the invention corresponds to a crystallizable fragment of an immunoglobulin. This Fc fragment can come from various immunoglobulins IgG1, IgG2, IgG3 or IgG4. It is responsible for the effector function of the immune response (WO2008/065543).

In one embodiment according to the invention, the Fc domain comes from an IgG4 immunoglobulin. In one particular embodiment, at least one point mutation or deletion has been introduced into the IgG4 Fc domain so as to increase the stability of the molecule, in particular by stabilizing the hinge region made up of the two Fc domains (Angla *et al.*, 1993, *Mol. Immunol.*, 30: 105-108), to reduce or eliminate the residual activity of the IgG4-Fc, in particular the effector activity (WO 97/09351), and to increase the homogeneity during the production of the recombinant protein. In particular, at least two point mutations, preferably three point mutations, have been introduced into the IgG4 Fc domain. In the Robo1-Fc L1, Robo1-Fc L2 and Robo1-Fc L3 molecules according to the invention, the preferred mutations are the following:

- S241P (Kabat numbering) in order to stabilize the disulphide-bridge bonding in the Fc hinge region;
- L248E (Kabat numbering) in order to eliminate the residual effector activity of the IgG4-Fc domain;
- absence of the C-terminal lysine in order to reduce the heterogeneity of the protein.

Robo1-Fc molecules according to the invention comprising the Ig1 and Ig2 domains of Robo1 isoform b, a linker and a mutated IgG4 domain as described above are Robo1-Fc L1, Robo1-Fc L2 and Robo1-Fc L3.

Robo1-Fc L1 corresponds to the protein of sequence SEQ ID NO.4, encoded by the nucleotide sequence SEQ ID NO.3.

Robo1-Fc L2 corresponds to the protein of sequence SEQ ID NO.6, encoded by the nucleotide sequence SEQ ID NO.5.

Robo1-Fc L1 and Robo1-Fc L2 differ by virtue of the nature of the linker.

Robo1-Fc L3 corresponds to the protein of sequence SEQ ID NO.24, encoded by the nucleotide sequence SEQ ID NO.23.

In one particular embodiment of the invention, one or more point mutations or deletions have been introduced in order to increase the homogeneity during

production. In particular, one amino acid, preferably two amino acids, have been truncated in the N-terminal position. Such a Robo-1-Fc molecule according to the invention is the Robo1-Fc L3 molecule, in which the two amino acids (Ser20 and Arg21) have been truncated and in which the amino acid Leu 22 has been fused to the signal peptide of interleukin 2.

The homogeneity of the Robo1-Fc molecules according to the invention is also increased by deleting the C-terminal Lys as previously described.

A subject of the invention is also proteins of which the protein sequence corresponds to the sequences SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6 or SEQ ID NO.24 or has at least 80%, 85%, 90%, 95% or 99% identity with the sequences SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6 or SEQ ID NO.24. These protein variants have the same biological activity as the proteins having the sequence SEQ ID NO.2, SEQ ID NO.4, SEQ ID NO.6 or SEQ ID NO.24, in particular their ability to interact with the proteins of the Slit family.

The Robo1-Fc proteins according to the invention can be produced by transfection of expression plasmids encoding these proteins into any cell type suitable for the expression of eukaryotic recombinant proteins: HEK293, CHO, etc., and then recovered in the culture supernatant and purified according to conventional methods.

Characterization of the Robo1-Fc L1, Robo1-Fc L2 and Robo1-Fc L3 proteins according to the invention has made it possible to confirm that they have the qualities required for their administration as a biotherapeutic agent.

A Robo1-Fc protein according to the invention has the ability to interact with a protein of the Slit family.

The Robo1-Fc proteins according to the invention specifically recognize the human Slit1, Slit2 and Slit3 proteins and the murine Slit2 protein, in particular by interaction with their D2 domain. Their affinity is similar with respect to the 3 members of the Slit family.

Another subject according to the invention corresponds to the nucleic acid molecules encoding the proteins according to the invention.

Thus, the nucleic acid molecules corresponding to the sequences SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5 or SEQ ID NO.23 or having at least 80%, 85%, 90%, 95% or 99% identity with the molecules having the sequence SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5 or SEQ ID NO.23 are part of the invention.

Another subject according to the invention consists of the use of a Robo1-Fc protein according to the invention for treating diseases in which a protein of the Slit family is overexpressed.

The proteins of the Slit family which can be targeted by the Robo1-Fcs according to the invention are Slit1, Slit2 or Slit3.

It has been shown that Robo1 can interact with the various members of the Slit family. Consequently, it is advantageous to note that the Robo1-Fc proteins according to the invention are capable of simultaneously inhibiting the signalling pathways mediated by Slit1, Slit2 and Slit3, which makes it possible to broaden the therapeutic spectrum in comparison with the antibodies which are specific for only one of these pathways.

In another embodiment, a Robo1-Fc protein is used for treating diseases in which a protein of the Slit family is overexpressed, by inhibiting angiogenesis without inhibiting endothelial cell proliferation. This anti-angiogenic activity linked to a vessel maturation defect is called “non-productive angiogenesis”.

Specifically, the experimental studies have shown that the Robo1-Fc molecules according to the invention are capable of inhibiting the formation of tubules, without inhibiting endothelial cell proliferation. They make it possible to very significantly reduce the tumour volume in a murine model of lung cancer.

In one preferred embodiment, the Robo1-Fc proteins that can be used for treating diseases in which a Slit protein is overexpressed are Robo1-Fc L1, Robo1-Fc L2 and Robo1-Fc L3, and the molecules which are derived therefrom, include, in particular, point mutations or deletions aimed at increasing the homogeneity during production without significantly modifying the biological properties of these molecules.

In general, the diseases that can be treated with a Robo-1-Fc protein according to

the invention are all the diseases in which inhibition of the Slit pathway can have a therapeutic effect, in particular the diseases in which a protein of the Slit family is overexpressed, and in particular those in which Slit2 is overexpressed.

Since the Robo1-Fc molecules according to the invention specifically bind the Slit2 molecule, it is interesting to note that said molecules are capable of simultaneously inhibiting the two pathways in which Slit2 is involved, namely the Robo1/Slit2 and Robo4/Slit2 pathways.

The Robo1-Fc proteins according to the invention can therefore be used for treating cancer, in particular pancreatic cancer, colon cancer, colorectal cancer with or without lymphatic metastasis, breast cancer, lung cancer and lung metastases, ovarian cancer, cervical cancer, melanomas, renal cancer, oral cancer, prostate cancer, liver cancer, etc.

In one particular embodiment, the Robo-Fc proteins are used for treating lung cancer and lung metastases.

The Robo1-Fc molecules according to the invention can also be used as an anticancer medicament as an alternative to or as a supplement to the current therapies.

In particular, these molecules can be administered in combination (optionally simultaneously) with anticancer compounds.

Another subject of the invention relates to a composition comprising a Robo1-Fc protein as defined above and one or more pharmaceutically acceptable excipients.

The Robo1-Fc proteins according to the invention can be formulated in pharmaceutical compositions with a view to topical, oral, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, etc., administration. Preferably, the pharmaceutical compositions contain pharmaceutically acceptable vehicles for an injectable formulation. They may in particular be isotonic sterile saline solutions (monosodium or disodium phosphate, sodium, potassium, calcium or magnesium chloride, etc., or mixtures of such salts), or dry, in particular freeze-dried, compositions which, by addition, as appropriate, of sterilized water or of physiological saline, allow the formation of injectable solutes.

Another aspect of the invention consists of the use of a Robo1-Fc molecule as a diagnostic tool for detecting the overexpression of a molecule of the Slit family in a patient. This is because it has been shown that the Slit pathway is implicated in many cancers. The provision of a test for evaluating a disturbance of the Slit signalling pathway is very useful for the purpose of selecting patients capable of responding to a treatment based on the administration of a Robo1-Fc molecule.

This diagnostic tool may be in the form of a ready-to-use kit, comprising a Robo1-Fc molecule in a form suitable for it to be brought into contact with a biological sample from a patient (blood, urine, tumour biopsy) liable to exhibit an overexpression of a Slit molecule. The Robo-Fc molecule can optionally be prelabelled, and the combination of Robo-Fc and Slit is detected so as to evaluate an increase in the expression of a Slit protein in the biological sample in comparison with a control sample. This kit can, for example, be in the form of an ELISA kit.

DESCRIPTION OF THE FIGURES

Figure 1: Expression plasmids for the Robo1-Fc L1, Robo1-Fc L2 and Robo1-Fc L3 proteins.

Figure 2: Evaluation of the interaction of the Robo1-Fc fusion protein variants with the Slit2 protein by ELISA.

Figure 3: Affinity of Robo1-Fc for HEK293 cells not expressing Slit2, measured by FACS.

Figure 4: Affinity of Robo1-Fc for HEK293 cells expressing Slit2, measured by FACS.

Figure 5: Pharmacokinetic profile of the Robo1-Fc proteins after an iv injection in mice. **A.** Administration of Robo1-Fc L1, **B.** Administration of Robo1-Fc L2.

Figure 6: Effect of the Robo1-Fc L1 molecule in a coculture test with endothelial cells and mesenchymal cells. **A.** Robo1-Fc L1 inhibits tubule formation in culture. **B.** Robo1-Fc L1 significantly inhibits VEGF-induced pseudotubule formation.

Figure 7: Evaluation of the effect of the Robo1-Fc L1 molecule on an *ex vivo* aortic ring model in mice. **A**: Description of the protocol for preparing an aortic ring and for measuring tubules. **B**: a. Control; b. Robo1-Fc Slit2-minus 500 µg/mL + VEGF 10 ng/mL; c. Robo1-Fc L1 500 µg/mL + VEGF 10 ng/mL.

EXAMPLES

Example 1: Preparation of the Robo1-Fc proteins

a. Constructs allowing the expression of the Robo1-Fc recombinant proteins used as biotherapeutic agents.

The Robo1-Fc recombinant proteins consist of a fusion between the first two immunoglobulin domains (Ig1-Ig2) of the human Robo1 protein, isoform b (NP_598334) and the Fc domain of human immunoglobulin G4 (hIgG4-Fc, SwissProt IGHG4_HUMAN).

In order to obtain the Robo1-Fc L1 construct, a fragment of the cDNA (SEQ ID NO.1) corresponding to the immunoglobulin (Ig) domains Ig1 and Ig2 of this protein (SEQ ID NO.2) followed by a GluArgProSerPheVal linker was amplified by PCR using the human foetal heart cDNA library (ref. HL5042T, Clontech). This amplified fragment was then cloned into the eukaryotic expression vector pXL4904 (described in Figure 1) such that the two Ig domains of Robo1 are expressed as a fusion with the Fc domain of human IgG4 in the C-terminal position. Three point mutations were introduced into the IgG4-Fc domain in order to obtain the following characteristics: S241P (Kabat numbering) in order to stabilize the disulphide-bridge bonding in the Fc hinge region; L248E in order to eliminate the residual effector activity of the IgG4-Fc domain; absence of the C-terminal lysine in order to reduce the heterogeneity of the protein. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.3. The recombinant protein obtained is called Robo1-Fc L1 and corresponds to the protein sequence SEQ ID NO.4.

In order to obtain the Robo1-Fc L2 construct, the same cDNA corresponding to the Ig1-Ig2 domains but without the linker mentioned was cloned into the eukaryotic expression vector pXL4909 (described in Figure 1), which allows the expression of these Ig domains as a fusion with the same Fc domain of IgG4 containing the 3 point mutations described in the construction of Robo1-Fc L1, but this time introducing a

GlyGlyGlyGlySer linker upstream of the Fc domain. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.5. The recombinant protein obtained is called Robo1-Fc L2 and corresponds to the protein sequence SEQ ID NO.6.

b. Construction of the Robo1-Fc proteins used as controls

In order to obtain the Robo1-Fc Slit2-minus construct, the cDNA previously cloned into the pXL4904 plasmid was modified by PCR so as to introduce the point mutations allowing the substitutions of the leucine at position 38 to glutamine and the phenylalanine at position 89 to tyrosine. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.7. The recombinant protein obtained is called Robo1-Fc Slit2-minus and corresponds to the protein sequence SEQ ID NO.8.

In order to obtain the Robo1-Fc heparin-minus construct, the cDNA cloned into the pXL4904 plasmid was modified by PCR so as to introduce the point mutations allowing the substitutions of the arginine at position 97 to aniline and the lysine at position 98 to alanine. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.9. The recombinant protein obtained is called Robo1-Fc heparin-minus and corresponds to the protein sequence SEQ ID NO. 10.

c. Production of the various Robo1-Fc proteins

The two proteins Robo1-Fc L1 and Robo1-Fc L2 were produced by transient transfection in the HEK293 line (FreeStyle 293-F cells ref 51-0029, Invitrogen, according to the supplier's recommendations) using the pXL4904 and pXL4909 plasmids, respectively, and the helper plasmids pXL4544 and pXL4551 allowing the expression of two N-glycan glycosylation enzymes, i.e. α-2,3-sialyltransferase and β-1,4-galactosyltransferase, as has been described in application WO2008/065543. These proteins were also produced by transfection in the CHO line (CHO-S cells, ref 11619-012, Invitrogen, according to the supplier's recommendations) using the pXL4904 and pXL4909 plasmids, respectively.

The Robo1-Fc L1 and Robo1-Fc L2 proteins expressed in the culture natant of the HEK293 cells were purified by chromatography on a protein A affinity column

(MabSelect ref. 17-5199-02, Amersham Biosciences) and elution in 20 mM NaCl / 100 mM acetic acid buffer, and then formulated in PBS buffer (ref. 14190-094, Invitrogen).

The Robo1-Fc Slit2-minus and Robo1-Fc heparin-minus recombinant proteins were produced and purified in the same way.

d. Physicochemical characterization of the Robo1-Fc recombinant proteins

SDS-PAGE and gel permeation analysis made it possible to show that the proteins were dimeric and more than 96% pure. Mass spectrometry analysis made it possible to demonstrate the identity of these proteins, the measured weight of the deglycosylated protein being in perfect agreement with the weight calculated *in silico.* Analysis of the monosaccharide composition and quantification of the N-glycan sialic acids as described by Saddic *et al.* 2002. (Methods Mol. Biol. 194: 23-36 and Anumula *et al.* 1998. Glycobiology 8: 685-694) made it possible to demonstrate that the proteins were sialylated to a very great extent. The results are given in table 1. It will be noted that the N-terminal analysis of the Robo1-Fc L1 and Robo1-Fc L2 molecules showed that these purified proteins contained a variable proportion (0 to 40%) of a form with the first 2 residues (Ser20 and Arg21) truncated.

Table 1: Robo1-Fc protein identity

	Robo1-Fc L1	**Robo1-Fc L2**
Weight (SDS-PAGE reducing conditions)	56 kDa	55 kDa
Weight (SEC, HPLC)	180 kDa	180 kDa
Weight (LC/MS after deglycosylation)	48812 Da	48410 Da
N-Glycan profile (HPLC)	highly sialylated 21.4% asialoglycans	highly sialylated 20.1% asialoglycans
Monosaccharide composition (HPLC)	complex N-glycans entirely fucosylated no O-glycans	complex N-glycans entirely fucosylated no O-glycans

Example 2: Preparation of the Slit proteins used as ligand

The cDNA encoding the human Slit2 protein corresponds to the reference protein NP_004778. Fragments of this cDNA were amplified by PCR using the human brain cDNA library (ref. 639300, Clontech).

The cDNA corresponding to the D2 domain was cloned into the eurkaryotic expression vector pXL4911 in order to express this domain containing a His tag in the C-terminal position. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.11. The recombinant protein obtained is called Slit2-D2 and corresponds to the protein sequence SEQ ID NO.12.

The cDNA corresponding to the D1-D2 domains was cloned into the eukaryotic expression vector pXL4912 in order to express these two domains containing a His tag in the C-terminal position. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.13. The recombinant protein obtained is called Slit2-D1D2 and corresponds to the protein sequence SEQ ID NO.14.

The cDNA corresponding to the extracellular part (Nt) of the Slit2 protein was cloned into the eukaryotic expression vector pXL5033 in order to express this protein with a His tag in the C-terminal position. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.15. The recombinant protein obtained is called Slit2-N and corresponds to the protein sequence SEQ ID NO.16.

The cDNA encoding the D2 domain of the murine Slit2 protein, and corresponding to the D2 domain of the described reference protein NP_848919, was obtained from the cDNA cloned into the pXL4911 plasmid. Four fragments making it possible to generate the five point mutations were generated by PCR with pXL4911 as template, and then these fragments were used as template to amplify the cDNA encoding the complete D2 domain by sequential PCR. The protein carries the Thr311Ser, Lys313Arg, Ile329Leu, Ile411Val and Pro418Ala mutations allowing it to be identical to the D2 domain of the murine Slit2 protein. This plasmid makes it possible to express the D2 domain of the murine Slit2 protein with a His tag in the C-terminal position. The cDNA sequence used to express this recombinant protein corresponds

to the sequence SEQ ID NO.17. The recombinant protein obtained is called mSlit2-D2 and corresponds to the protein sequence SEQ ID NO.18.

The cDNA encoding the human Slit1 protein corresponds to the described reference protein NP_003052. A fragment of this cDNA was amplified by PCR using the human brain cDNA library (ref. 639300, Clontech). The cDNA corresponding to the D2 domain was cloned into the eukaryotic expression vector pXL5020 in order to express this domain containing a His tag in the C-terminal position. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.19. The recombinant protein obtained is called Slit1-D2 and corresponds to the protein sequence SEQ ID NO.20.

The cDNA encoding the human Slit3 protein corresponds to the described reference protein NP_003053. A fragment of this cDNA was amplified by PCR using the human brain cDNA library (ref. 639300, Clontech). The cDNA corresponding to the D2 domain was cloned into the eukaryotic expression vector pXL5021 in order to express this domain containing a His tag in the C-terminal position. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.21. The recombinant protein obtained is called Slit3-D2 and corresponds to the protein sequence SEQ ID NO.22.

The three proteins called Slit2-D2, Slit2-D1D2 and Slit2-N were produced by transient transfection in the HEK293 line (FreeStyle 293-F cells according to the supplier's recommendations, Invitrogen) using the pXL4911 plasmid (respectively, pXL4912 or pXL5033).

The Slit2-D2 and Slit2-D1D2 proteins expressed in the culture supernatant of the HEK293 cells were purified by chromatography on an Ni-chelating sepharose column (ref. 17-0409-03, Amersham Biosciences) and elution in imidazole buffer and then formulated in PBS buffer (ref. 14190-094, Invitrogen) adjusted to 1M NaCl. Mass spectrometry analysis (LC/MS) made it possible to demonstrate the identity of these proteins.

The three proteins called mSlit2-D2, Slit1-D2 and Slit3-D2 were produced, purified and characterized in a comparable manner.

Example 3: Study of the affinity of the Robo1-Fc recombinant proteins for the Slit proteins and for heparin by means of three methods: ELISA, SPR and FACS

a. Affinity of the Robo1-Fc proteins for heparin

In order to determine the affinity of the Robo1-Fc constructs for heparin, 2 mg of Robo1-Fc protein, purified and formulated in 10 mM phosphate, pH 7.0, were chromatographed on a heparin column (1 mL HiTrap Heparin-Sepharose HP, GE Heathcare) by elution with a linear gradient of NaCl of from 0 to 1.5 M.

Table 2 indicates the NaCl concentration of 448 mM necessary for eluting the Robo1-Fc L1 protein as described in the literature (Fukuhara, N. et al. 2008 J. Biol. Chem. 283 p16226-16234).

Table 2: Affinity of Robo1-Fc for heparin

Robo1-Fc construct	**Detachment from the heparin column [NaCl], mM**
Robo1-Fc L1	448
Robo1-Fc Heparin-minus	No binding

These results show that the Robo1-Fc heparin-minus protein is not retained on this column, and therefore that it no longer has any affinity for heparin. This protein is therefore a heparin-negative mutant.

b. Evaluation of the interaction of the Robo1-Fc protein variants with the D2 domain of the human Slit2 protein

This example describes the interaction of the two variants called Robo1-Fc L1 and Robo1-Fc L2 with their natural ligand (in these experiments, the D2 domain of human Slit2) by ELISA assay.

The human Slit2-D2 protein was bound to Immulon-4 enzyme-linked plates (VWR

Scientific Inc. Swedesboro, NJ). A concentration range (from 20 µg/mL to 0.02 µg/mL) of the Robo1-Fc L1 and Robo1-Fc L2 variants was added and then detected by means of the peroxidase-conjugated goat anti-human IgG antibody (Sigma; ref. A0170, dilution to 1:50 000). Visualization was carried out with the TMB-H_2O_2 substrate (Interchim; ref UP664780) and the measurements were carried out with a plate reader at 450 nm. The results are reported in Figure 2. They show that the two variants Robo1-Fc L1 and L2 specifically interact with the human Slit2 protein (in particular with the D2 domain).

c. Evaluation of the interaction of the Robo1-Fc protein with the human variants of the Slit family, namely Slit1 and Slit3

This example describes the interaction of the Robo1-Fc L1 fusion protein with the Slit1-D2, Slit2-D2 and Slit3-D2 variants by ELISA assay.

The D2 domain of the human Slit variants was bound to Immulon-4 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). A concentration range (from 1 µg/mL to 0.001 µg/mL) of the Robo1-Fc L1 fusion protein was added and then detected using the peroxidase-conjugated goat anti-human IgG antibody (Sigma; ref. A0170, dilution to 1:50 000). Visualization was carried out with the TMB-H_2O_2 substrate (Interchim; ref UP664780) and the measurements were carried out with a plate reader at 450 nm. Similarly, the Robo1-Fc Slit2-minus variant, which is mutated at the level of the Slit2-binding site, was evaluated according to a concentration range (from 20 µg/mL to 0.02 µg/mL) by ELISA assay under the same conditions described above. The results are reported in table 3 below.

Table 3: Affinity of Robo1-Fc for the human variants of the Slit protein

Slit protein (ligand)	**Robo1-Fc protein**	**EC50 (µg/mL)**	**CV (%)**
Slit2-D2	Robo1-Fc L1	1.32 E-01	3.3
Slit1-D2	Robo1-Fc L1	7.88 E-02	3.9
Slit3-D2	Robo1-Fc L1	2.60 E-01	12
Slit2-D2	Robo1-Fc Slit2-minus	1.78 E+01	18

These results show that the Robo1-Fc protein interacts specifically with the three proteins of the family, Slit1, Slit2 and Slit3 (in particular with their D2 domain).

In addition, the Robo1-Fc Slit2-minus protein no longer has affinity for heparin and it is therefore a heparin-negative mutant.

d. Evaluation of the interaction of the Robo1-Fc protein with the murine Slit2 protein

This example describes the interaction of the Robo1-Fc L1 fusion protein with the murine protein mSlit2-D2 by ELISA assay.

The murine protein mSlit2-D2 was bound to an Immulon-4 enzyme-linked plate (VWR Scientific Inc. Swedesboro, NJ). A concentration range (from 2 µg/mL to 0.002 µg/mL) of the Robo1-Fc L1 fusion protein was added and then detected using the peroxidase-conjugated goat anti-human IgG antibody (Sigma; ref. A0170, dilution to 1:50 000). Visualization was carried out with the TMB-H_2O_2 substrate (Interchim; ref UP664780) and the measurements were carried out with a plate reader at 450 nm. The results are reported in table 4 below.

Table 4 : Affinity of Robo1-Fc L1 for the murine Slit2 protein

Protein studied	**EC50 (µg/mL)**	**CV (%)**
mSlit2-D2	2.21 E-01	18

These results show that the Robo1-Fc protein interacts specifically with the murine Slit2 protein

e. Affinity of Robo1-Fc for the Slit protein measured by SPR

This example describes the determination of the affinity constant of the Robo1-Fc L1 fusion protein with the human Slit2 protein (in this experiment, Slit2-D2) by SPR (Surface Plasmon Resonance; BIAcore 2000). The interaction between the Robo1-Fc protein and the human Slit2 protein was analysed after having bound the Robo1-Fc fusion protein to a CM5 chip. The kinetic measurements were carried out

according to the protocol of Canziani *et al.* (2004. Anal. Biochem. 325: 301-307).

Table 5: Affinity constant of Robo-Fc L1 with human Slit2-D2 by SPR (steady-state analysis)

Protein	K_D (nM)
Robo1-Fc L1	32

A second method, which consists in determining the affinity constant between the Robo1-Fc L1 fusion protein and the human Slit2 protein, was analysed after having bound the Slit2-D2 protein to the CM5 chip. The kinetic measurements are carried out according to the protocol of Canziani *et al.* (2004. Anal. Biochem. 325: 301-307) using the Scatchard method according to a model with two non-equivalent binding sites.

Table 6: Affinity constant of Robo1-Fc with human Slit2-D2 by SPR according to the two-phase Scatchard model

Robo1-Fc L1	K_D (nM)
High-affinity site	K_{D1}: 1.5
Low-affinity site	K_{D2}: 160

f. Affinity of Robo1-Fc for Slit measured by FACS

This example describes the affinity of the Robo1-Fc protein on HEK293 mammalian cells expressing Slit2.

The HEK293 cells described and used as in example 1 were transfected either with a ballast plasmid, having no cDNA that encodes in the mammalian cell, or the pXL4911 plasmid encoding the Slit2-D2 protein, or the pXL4912 plasmid encoding the Slit2-D1D2 protein, or pXL5033 encoding the Slit2-N protein described in example 2. The cells were distributed into 96-well plates 48 hours post-transfection, and the Robo1-Fc protein was added in a concentration range of from 0.01 to 3 mg/L for 30 min at 4°C. The Robo1-Fc protein is either the Robo1-Fc L1 biotherapeutic

agent, or the Robo1-Fc Slit2-minus mutant, or the Robo1-Fc heparin-minus mutant. The cells were washed and the anti-human Fc antibody labelled with Alexa 488 (ref: A-11013, Invitrogen) was incubated for 30 min at 4°C. The labelled HEK293 cells are then quantified by FACS (Geomean).

Figure 3 describes the binding of the HEK293 cells to the Robo1-Fc protein, via the fluorescence measured by the FACS in the absence of Slit2 expression. The Robo1-Fc protein and also the Robo1-Fc Slit2-minus mutant bind to the HEK293 cells, whereas the Robo1-Fc heparin-minus mutant does not bind. Robo1-Fc therefore binds partly to the HEK293 cells via heparin binding at the low Robo1-Fc concentrations of 0.3 to 0.03 mg/L.

Figure 4 describes the binding of the HEK293 cells to the Robo1-Fc protein, via the fluorescence measured by FACS when Slit2-N is expressed by transient transfection. Only the Robo1-Fc protein binds to the HEK293 cells expressing Slit2-N. The Robo1-Fc Slit2-minus and Robo1-Fc heparin-minus mutants do not bind (or virtually not) in the Robo1-Fc concentration range of 3.0 to 0.3 mg/L, compared with the biotherapeutic Robo1-Fc L1 protein.

Table 7 describes the affinity constants measured by FACS for the Robo1-Fc protein when the Slit2-N, Slit2-D1D2 or Slit2-D2 proteins are expressed in the HEK293 line.

Table 7: Affinity of Robo1-Fc for the Slit2 protein on cells by FACS

Ligand Robo1-Fc	**Protein expressed transiently in HEK293**	**K_D (nM)**
Robo1-Fc L1	Slit2-N	1.2
	Slit2-D1D2	0.98
	Slit2-D2	Very weak binding
Robo1-Fc Heparin-minus	Slit2-N	43
	Slit2-D1D2	41
Robo1-Fc Slit2-minus	Slit2-N	No binding

As in the previous examples, the Robo1-Fc Slit2-minus mutant proved to be Slit2-negative and the Robo1-Fc heparin-minus mutant has a weaker affinity for Slit2 than the biotherapeutic protein.

Robo1-Fc binds to Slit2-N and Slit2-D1D2 expressed by the HEK293 cells with comparable affinities which are better than the affinity with Slit2-D2.

Example 4: Pharmacokinetic properties of the Robo1-Fc L1 and Robo1-Fc L2 proteins

This example describes the pharmacokinetic profile and the plasma concentration of the Robo1-Fc protein injected once in mice intravenously (iv).

Three Balb/C mice (for each time) were injected, via the caudal vein, with each of the Robo1-Fc proteins at 2.5 mg/mL in a proportion of 100 µL/10 g (≈ 25 mg/kg). At the predetermined times (0.5, 1, 6, 24, 48 and 72 h after administration), the mice were anaesthetized, and blood was sampled and collected in a tube containing 10 µL of citrate (CPD-A, C-4431 Sigma) and 2 µL of protease inhibitors (Complete Protease Inhibitor Mix, Roche Molecular Biochemical). The tubes were centrifuged and the plasma samples were collected and frozen at -20°C.

The wells of 96-well plates were coated with the Slit2 protein (Slit2-D2), and the plasma samples, diluted to 1/5000 and 1/20 000, were brought into contact for one hour at 37°C. The peroxidase-conjugated anti-human Fc antibody (ref. 31413, Pierce) was subsequently incubated and then visualized with TMB-H_2O_2 (ref UP664780, Interchim) and the absorbance was read at 450 nm. A calibration range was prepared with each purified Robo1-Fc protein.

The plasma concentrations of the Robo1-Fc L1 and Robo1-Fc L2 proteins are represented in Figure 5. The pharmacokinetic parameters are described in the following table 8 and show that the protein is stable after injection in mice.

Table 8: Pharmacokinetic parameters of the Robo1-Fc proteins after iv injection in mice

Protein at 25 mg/kg	C_0 µg/mL	$T_{1/2}$ h	AUC (0-last) µg.h/mL	AUC (0-24h) µg.h/mL	Cl mL/H/kg	Vdss mL/kg
Robo1-Fc L1	203	158	3655	1879	2.2	470
Robo1-Fc L2	198	142	3973	2042	2.2	417

Example 5: Description of the Robo1-Fc biotherapeutic protein improved with respect to its homogeneity in the N-terminal position

This example describes the expression plasmid, the production and the physicochemical characterization of another Robo1-Fc protein, called Robo1-Fc L3, which is different from the Robo1-Fc L1 protein by virtue of the absence of the first two residues Ser20 and Arg21.

The cDNA cloned into the pXL4904 plasmid was modified by PCR in order to eliminate the Ser20 and Arg21 codons, and to fuse the next codon (Leu22) to the coding sequence of the peptide signal of interleukin 2. The pXL5004 expression plasmid was then generated, see Figure 1. The cDNA sequence used to express this recombinant protein corresponds to the sequence SEQ ID NO.23.

The Robo1-Fc L3 protein was produced, purified and characterized as described in example 1. The N-terminal analysis showed that this purified protein was perfectly homogeneous. The recombinant protein obtained is called Robo1-Fc L3 and corresponds to the protein sequence SEQ ID NO.24.

Example 6: Evaluation of the interaction of the Robo1-Fc L3 protein with the human Slit2 protein

This example describes the interaction of the Robo1-Fc L3 fusion protein with the human Slit2 protein (Slit2-D2) by ELISA assay.

The human Slit2-D2 protein was bound to Immulon-4 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). A concentration range (from 1 µg/mL to 0.001 µg/mL) of the Robo1-Fc L3 fusion protein was added and then detected by means of the peroxidase-conjugated goat anti-human IgG antibody (Sigma; ref. A0170, dilution to 1:50 000). The visualization was carried out with the TMB-H_2O_2 substrate (Interchim; ref UP664780) and the measurements were carried out with a plate reader at 450 nm. The results obtained are reported in table 9 below.

Table 9: Affinity of the Robo1-Fc L3 protein for the Slit2 protein – Comparison with the Robo1-Fc L1 protein

Proteins studied	**EC50 (µg/ml)**	**CV (%)**
Robo1-Fc L1	0.13	3.3
Robo1-Fc L3	0.17	4.4

These results show that the affinities of the two variants Robo1-Fc L1 and Robo1-Fc L3 for the Slit2-D2 protein are comparable.

Example 7: Evaluation of the activity of the Robo-Fc protein on neovascularization

a. *In vitro* endothelial cell and fibroblast coculture model: specific activity of the Robo1-Fc L1 molecule

The *in vitro* angiogenesis model corresponds to a rearrangement of human vein endothelial cells on a monolayer of human dermal fibroblasts. Briefly, the fibroblasts (Lonza) are seeded into 24-well plates (Becton Dickinson) at 40 000 cells/well in 1 ml of medium. After 3 days of proliferation (D3), human vein endothelial cells (HUVEC-Lonza) are seeded onto the fibroblast cell monolayer at 10 000 cells/well in 500 µl of EGM® medium (endothelial basal medium, Lonza) + 2% FCS (foetal calf serum – Lonza) + 10 µg/ml hEGF (recombinant human epidermal growth factor – Lonza). The cells are stimulated with 30 ng/mL of VEGF (R&D Systems), with the Robo1-Fc L1 molecule or with a Robo1-Fc Slit2-minus negative control at the

concentration of 500 µg/ml (D3 to D9). After 3 days, the medium is replaced and the wells are stimulated according to the conditions of the experiment.

After 2 days, the cells are fixed with ethanol and labelled with an anti-CD31 antibody specific for HUVECs, followed by an anti-alkaline phosphatase antibody, and then visualized with an alkaline phosphatase substrate (D11). A quantification of the tubules labelled with the anti-CD31 antibody is carried out by means of image acquisitions made under a microscope (×4 objective) and the length of the pseudotubules is analysed using image analysis software (Biocom Visiolab 2000 software) (Figure 6).

In this *in vitro* angiogenesis assay, Robo1-Fc L1 (500 µg/ml) shows an inhibitory activity on the formation of the tubules formed by the HUVECs. This inhibition amounts to 82% and it is statistically significant compared with the effect obtained with the Robo1-Fc Slit2-minus molecule (negative control).

b. *Ex vivo* mouse aortic ring model: specific activity of the Robo1-Fc L1 molecule

The Robo1-Fc L1 molecuel was evaluated in a mouse aortic ring model. Briefly, mouse aortas are removed and cleaned, and cut into sections of 1 mm (D0). These rings are embedded in rat collagen in the presence of VEGF at 10 ng/ml, of the Robo1-Fc L1 molecule at the concentration of 500 µg/ml or of a Robo1-Fc Slit2-minus negative control at the concentration of 500 µg/ml. Tubules will form from the ring, thus mimicking *in vitro*, the formation of neovessels. After 6 days, a quantification of the labelled tubules is carried out by means of image acquisitions made under a microscope (×3 objective) (Figure 7A) and the length of the pseudotubules is analysed using image analysis software (Biocom Visiolab software 2000) (Figure 7).

Under these experimental conditions, Robo1-Fc L1 (500 µg/ml) shows a strong inhibitory activity on the formation of the tubules formed, in comparison with the Robo1-Fc Slit2-minus molecule used as a negative control.

These results suggest that Robo1-Fc L1 is capable of inhibiting the formation of neovessels without inhibiting endothelial cell proliferation. This anti-angiogenic activity linked to a vessel maturation defect is called “non-productive angiogenesis”.

Example 8: Evaluation of the Robo1-Fc L1 protein in a lung tumour model in mice

The Robo1-Fc L1 molecule was evaluated in a model of a lung cancer tumour in C57/Bl6 mice.

a. Murine lung tumour model

In order to establish the murine lung tumour model, 8-week-old female C57/Bl6 mice were anaesthetized. The area at the level of the left scapula of the mouse was shaved and disinfected. A 1 cm incision was made above the scapula.

The cells to be injected are derived from a Lewis lung carcinoma tumour line (ATCC, CRL-1642). The cells were mixed with Matrigel® in a ratio of 1 vol of Matrigel to 4 vol of cells. The cell concentration was 62 500 cells/ml. The cells were injected into the lung at a rate of 20 µl per mouse, and then the wound was sutured.

After 23 days, the mice were euthanized. The ribcage was opened up, and the left lung and the mediastinal lymph nodes were removed. The tumour present on the left lung was measured using an electronic calliper rule in order to determine the tumour volume according to the formula: $l2 \times L \times 0.52$. The mediastinal lymph nodes are weighed. The results are expressed as mean value ± standard deviation from the mean. The statistical analysis was carried out by means of a parametric Student's test.

b. Treatment of the mice bearing a lung tumour with the Robo1-Fc recombinant protein

The treatment using the Robo1-Fc protein was carried out as follows: a preparation containing the Robo1-Fc protein was injected at the dose of 25 mg/kg/day, intravenously, on D10, D14, D17 and D21 post-injection of the tumour cells. The control group was injected with PBS buffer (10 ml/kg).

c. Results

On D23, the mean volume of the tumours obtained in the group treated with the Robo1-Fc recombinant protein was 21.45 ± 2.16 mm^3; the mean volume of the tumours obtained in the control group was 39.93 ± 8.41 mm^3. The reduction in

tumour volume in the animals treated with the Robo1-Fc protein is 46%. This difference is statistically significant ($p<0.05$). The mean weight of the mediastinal lymph nodes (metastatic lymph nodes) obtained in the group treated with the Robo1-Fc protein is 12.50 ± 1.26 mg. The mean weight of the mediastinal lymph nodes obtained in the control group is 30.67 ± 7.69 mg. The reduction in weight of the mediastinal lymph nodes for the group treated with the Robo1-Fc protein is 59% at the limit of significance ($p=0.07$).

Claims

1. Robo-Fc recombinant protein comprising the extracellular domain of the Robo1 protein or a part of this domain, a linker and an immunoglobulin Fc domain, in which said extracellular domain comes from isoform b of the Robo1 protein.

2. Protein according to Claim 1, in which the extracellular domain of Robo1 comprises the Ig1 and Ig2 immunoglobulin domains.

3. Protein according to Claim 2, in which the extracellular domain of Robo1 has at least 80% identity with the sequence SEQ ID NO.2.

4. Protein according to one of the preceding claims, in which the Fc domain comes from human immunoglobulin G4.

5. Protein according to Claim 4, in which the Fc domain contains at least one point mutation aimed at increasing the stability of the protein and/or at eliminating the residual effector activity of the Fc domain and/or at increasing the homogeneity during its production.

6. Protein according to Claim 5, in which the Fc domain comprises the S241P and L248E mutations and in which the lysine located in the C-terminal position is absent.

7. Protein according to one of Claims 2 to 4, in which the amino acids Ser20 and Arg21 have been deleted so as to increase the homogeneity during its production.

8. Protein according to one of Claims 1 to 4, of which the sequence has at least 80% identity with the sequence SEQ ID NO. 4, SEQ ID NO.6 or SEQ ID NO. 24.

9. Nucleic acid molecule encoding one of the proteins as defined in Claims 1 to 8.

10. Nucleic acid molecule corresponding to the sequence SEQ ID NO.1, SEQ

ID NO.3, SEQ ID NO.5 or SEQ ID NO.23 or having at least 80% identity with the molecules having the sequence SEQ ID NO.1, SEQ ID NO.3, SEQ ID NO.5 or SEQ ID NO.23.

11. Robo1-Fc recombinant protein according to one of Claims 1 to 8, for use as a medicament.

12. Protein for use according to Claim 11 in the treatment of diseases in which a protein of the Slit family is overexpressed.

13. Protein for use according to Claim 11 for treating cancer.

14. Protein for use according to either of Claims 12 and 13, which does not inhibit endothelial cell proliferation.

15. Protein for use according to Claim 13 for treating lung cancer or lung metastases.

16. Protein for use according to one of Claims 11 to 15, this protein deriving from isoform b of the Robo1 protein.

17. Protein for use according to Claim 16, this protein being as defined in Claims 2 to 8.

18. Pharmaceutical composition comprising a Robo1-Fc recombinant protein as defined in Claims 1 to 8 and at least one excipient.

19. Use of a Robo1-Fc molecule according to the invention as a diagnostic tool for detecting the overexpression of a molecule of the Slit family in a patient.

SEQUENCE LISTING

<110> SANOFI-AVENTIS

<120> Robo1-Fc fusion protein and use thereof for treating tumours.

<130> FR2009-116 PCT

<160> 24

<170> PatentIn version 3.3

<210> 1
<211> 660
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(660)

<400> 1

```
atg att gcg gag ccc gct cac ttt tac ctg ttt gga tta ata tgt ctc       48
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                  10                  15

tgt tca ggc tcc cgt ctt cgt cag gaa gat ttt cca cct cgc att gtt       96
Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

gaa cac cct tca gac ctg att gtc tca aaa gga gaa cct gca act ttg      144
Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

aac tgc aaa gct gaa ggc cgc ccc aca ccc act att gaa tgg tac aaa      192
Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

ggg gga gag aga gtg gag aca gac aaa gat gac cct cgc tca cac cga      240
Gly Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg
65                  70                  75                  80

atg ttg ctg ccg agt gga tct tta ttt ttc tta cgt ata gta cat gga      288
Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
                85                  90                  95

cgg aaa agt aga cct gat gaa gga gtc tat gtc tgt gta gca agg aat      336
Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

tac ctt gga gag gct gtg agc cac aat gca tcg ctg gaa gta gcc ata      384
Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

ctt cgg gat gac ttc aga caa aac cct tcg gat gtc atg gtt gca gta      432
Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

gga gag cct gca gta atg gaa tgc caa cct cca cga ggc cat cct gag      480
Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

ccc acc att tca tgg aag aaa gat ggc tct cca ctg gat gat aaa gat      528
Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175
```

```
gaa aga ata act ata cga gga gga aag ctc atg atc act tac acc cgt      576
Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

aaa agt gac gct ggc aaa tat gtt tgt gtt ggt acc aat atg gtt ggg      624
Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

gaa cgt gag agt gaa gta gcc gag ctg act gtc tta                      660
Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu
    210                 215                 220
```

<210> 2
<211> 220
<212> PRT
<213> Homo sapiens

<400> 2

```
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                   10                  15

Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

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

Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
                85                  90                  95

Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175

Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190
```

```
Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205


Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu
    210                 215                 220


<210>  3
<211>  1365
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(1365)

<400>  3
atg att gcg gag ccc gct cac ttt tac ctg ttt gga tta ata tgt ctc       48
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                   10                  15

tgt tca ggc tcc cgt ctt cgt cag gaa gat ttt cca cct cgc att gtt       96
Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

gaa cac cct tca gac ctg att gtc tca aaa gga gaa cct gca act ttg      144
Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

aac tgc aaa gct gaa ggc cgc ccc aca ccc act att gaa tgg tac aaa      192
Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

ggg gga gag aga gtg gag aca gac aaa gat gac cct cgc tca cac cga      240
Gly Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg
65                  70                  75                  80

atg ttg ctg ccg agt gga tct tta ttt ttc tta cgt ata gta cat gga      288
Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
                85                  90                  95

cgg aaa agt aga cct gat gaa gga gtc tat gtc tgt gta gca agg aat      336
Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

tac ctt gga gag gct gtg agc cac aat gca tcg ctg gaa gta gcc ata      384
Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

ctt cgg gat gac ttc aga caa aac cct tcg gat gtc atg gtt gca gta      432
Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

gga gag cct gca gta atg gaa tgc caa cct cca cga ggc cat cct gag      480
Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

ccc acc att tca tgg aag aaa gat ggc tct cca ctg gat gat aaa gat      528
Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175

gaa aga ata act ata cga gga gga aag ctc atg atc act tac acc cgt      576
Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

aaa agt gac gct ggc aaa tat gtt tgt gtt ggt acc aat atg gtt ggg      624
```

```
Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

gaa cgt gag agt gaa gta gcc gag ctg act gtc tta gag aga cca tca      672
Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser
    210                 215                 220

ttt gtg gag tcc aag tac ggc cct cct tgc cct ccc tgc cct gcc cct      720
Phe Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

gag ttc gag ggc gga cct agc gtg ttc ctg ttc cct cct aag cct aag      768
Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

gac acc ctg atg atc tcc cgg acc cct gag gtg acc tgt gtg gtg gtg      816
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

gac gtg tcc cag gag gac cct gag gtc cag ttc aac tgg tac gtg gac      864
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
        275                 280                 285

ggc gtg gag gtg cac aac gcc aag acc aag cct cgg gag gag cag ttc      912
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    290                 295                 300

aat tcc acc tac cgg gtg gtg tct gtg ctg acc gtg ctg cac cag gac      960
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

tgg ctg aac ggc aaa gaa tac aag tgt aag gtc tcc aac aag ggc ctg     1008
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
                325                 330                 335

ccc tcc tcc atc gag aaa acc atc tcc aag gcc aag ggc cag cct agg     1056
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

gag cct cag gtg tac acc ctg cct cct agc cag gaa gag atg acc aag     1104
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
        355                 360                 365

aac cag gtg tcc ctg acc tgt ctg gtg aag ggc ttc tac cct tcc gac     1152
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

atc gcc gtg gag tgg gag tcc aac ggc cag cct gag aac aac tac aag     1200
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

acc acc cct cct gtg ctg gac tcc gac ggc tcc ttc ttc ctg tac tcc     1248
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

agg ctg acc gtg gac aag tcc cgg tgg cag gag ggc aac gtc ttt tcc     1296
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
            420                 425                 430

tgc tcc gtg atg cac gag gcc ctg cac aac cac tac acc cag aag tcc     1344
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

ctg tcc ctg tct ctg ggc tga                                        1365
Leu Ser Leu Ser Leu Gly
    450
```

<210> 4
<211> 454
<212> PRT
<213> Homo sapiens

<400> 4

Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1 5 10 15

Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
20 25 30

Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
35 40 45

Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
50 55 60

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

Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
85 90 95

Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
100 105 110

Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
115 120 125

Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
130 135 140

Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145 150 155 160

Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
165 170 175

Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
180 185 190

Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
195 200 205

Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser
210 215 220

Phe Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
290 295 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
325 330 335

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Leu Gly
450

<210> 5
<211> 1362
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1362)

<400> 5
atg att gcg gag ccc gct cac ttt tac ctg ttt gga tta ata tgt ctc 48
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu

```
1               5                   10                  15

tgt tca ggc tcc cgt ctt cgt cag gaa gat ttt cca cct cgc att gtt      96
Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

gaa cac cct tca gac ctg att gtc tca aaa gga gaa cct gca act ttg     144
Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

aac tgc aaa gct gaa ggc cgc ccc aca ccc act att gaa tgg tac aaa     192
Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

ggg gga gag aga gtg gag aca gac aaa gat gac cct cgc tca cac cga     240
Gly Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg
65                  70                  75                  80

atg ttg ctg ccg agt gga tct tta ttt ttc tta cgt ata gta cat gga     288
Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
                85                  90                  95

cgg aaa agt aga cct gat gaa gga gtc tat gtc tgt gta gca agg aat     336
Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

tac ctt gga gag gct gtg agc cac aat gca tcg ctg gaa gta gcc ata     384
Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

ctt cgg gat gac ttc aga caa aac cct tcg gat gtc atg gtt gca gta     432
Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

gga gag cct gca gta atg gaa tgc caa cct cca cga ggc cat cct gag     480
Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

ccc acc att tca tgg aag aaa gat ggc tct cca ctg gat gat aaa gat     528
Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175

gaa aga ata act ata cga gga gga aag ctc atg atc act tac acc cgt     576
Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

aaa agt gac gct ggc aaa tat gtt tgt gtt ggt acc aat atg gtt ggg     624
Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

gaa cgt gag agt gaa gta gcc gag ctg act gtc tta gga ggc gga gga     672
Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Gly Gly Gly Gly
    210                 215                 220

tcc gag tcc aag tac ggc cct cct tgc cct ccc tgc cct gcc cct gag     720
Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

ttc gag ggc gga cct agc gtg ttc ctg ttc cct cct aag cct aag gac     768
Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

acc ctg atg atc tcc cgg acc cct gag gtg acc tgt gtg gtg gtg gac     816
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

gtg tcc cag gag gac cct gag gtc cag ttc aac tgg tac gtg gac ggc     864
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
```

```
        275                 280                 285

gtg gag gtg cac aac gcc aag acc aag cct cgg gag gag cag ttc aat      912
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
    290                 295                 300

tcc acc tac cgg gtg gtg tct gtg ctg acc gtg ctg cac cag gac tgg      960
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320

ctg aac ggc aaa gaa tac aag tgt aag gtc tcc aac aag ggc ctg ccc     1008
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
                325                 330                 335

tcc tcc atc gag aaa acc atc tcc aag gcc aag ggc cag cct agg gag     1056
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

cct cag gtg tac acc ctg cct cct agc cag gaa gag atg acc aag aac     1104
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
        355                 360                 365

cag gtg tcc ctg acc tgt ctg gtg aag ggc ttc tac cct tcc gac atc     1152
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

gcc gtg gag tgg gag tcc aac ggc cag cct gag aac aac tac aag acc     1200
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

acc cct cct gtg ctg gac tcc gac ggc tcc ttc ttc ctg tac tcc agg     1248
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
                405                 410                 415

ctg acc gtg gac aag tcc cgg tgg cag gag ggc aac gtc ttt tcc tgc     1296
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
            420                 425                 430

tcc gtg atg cac gag gcc ctg cac aac cac tac acc cag aag tcc ctg     1344
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

tcc ctg tct ctg ggc tga                                            1362
Ser Leu Ser Leu Gly
    450


<210>  6
<211>  453
<212>  PRT
<213>  Homo sapiens

<400>  6

Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                   10                  15


Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30


Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45


Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60
```

```
Gly Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg
65                  70                  75                  80

Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
                85                  90                  95

Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175

Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Gly Gly Gly Gly
    210                 215                 220

Ser Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
    290                 295                 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
                325                 330                 335
```

```
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
        355                 360                 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
                405                 410                 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
            420                 425                 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

Ser Leu Ser Leu Gly
    450
```

<210> 7
<211> 1365
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1365)

<400> 7

```
atg att gcg gag ccc gct cac ttt tac ctg ttt gga tta ata tgt ctc       48
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                   10                  15

tgt tca ggc tcc cgt ctt cgt cag gaa gat ttt cca cct cgc att gtt       96
Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

gaa cac cct tca gac cag att gtc tca aaa gga gaa cct gca act ttg      144
Glu His Pro Ser Asp Gln Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

aac tgc aaa gct gaa ggc cgc ccc aca ccc act att gaa tgg tac aaa      192
Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

ggg gga gag aga gtg gag aca gac aaa gat gac cct cgc tca cac cga      240
Gly Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg
65                  70                  75                  80

atg ttg ctg ccg agt gga tct tta tat ttc tta cgt ata gta cat gga      288
Met Leu Leu Pro Ser Gly Ser Leu Tyr Phe Leu Arg Ile Val His Gly
                85                  90                  95
```

```
cgg aaa agt aga cct gat gaa gga gtc tat gtc tgt gta gca agg aat      336
Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

tac ctt gga gag gct gtg agc cac aat gca tcg ctg gaa gta gcc ata      384
Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

ctt cgg gat gac ttc aga caa aac cct tcg gat gtc atg gtt gca gta      432
Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

gga gag cct gca gta atg gaa tgc caa cct cca cga ggc cat cct gag      480
Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

ccc acc att tca tgg aag aaa gat ggc tct cca ctg gat gat aaa gat      528
Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175

gaa aga ata act ata cga gga gga aag ctc atg atc act tac acc cgt      576
Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

aaa agt gac gct ggc aaa tat gtt tgt gtt ggt acc aat atg gtt ggg      624
Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

gaa cgt gag agt gaa gta gcc gag ctg act gtc tta gag aga cca tca      672
Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser
    210                 215                 220

ttt gtg gag tcc aag tac ggc cct cct tgc cct ccc tgc cct gcc cct      720
Phe Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

gag ttc gag ggc gga cct agc gtg ttc ctg ttc cct cct aag cct aag      768
Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

gac acc ctg atg atc tcc cgg acc cct gag gtg acc tgt gtg gtg gtg      816
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

gac gtg tcc cag gag gac cct gag gtc cag ttc aac tgg tac gtg gac      864
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
        275                 280                 285

ggc gtg gag gtg cac aac gcc aag acc aag cct cgg gag gag cag ttc      912
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    290                 295                 300

aat tcc acc tac cgg gtg gtg tct gtg ctg acc gtg ctg cac cag gac      960
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

tgg ctg aac ggc aaa gaa tac aag tgt aag gtc tcc aac aag ggc ctg     1008
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
                325                 330                 335

ccc tcc tcc atc gag aaa acc atc tcc aag gcc aag ggc cag cct agg     1056
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

gag cct cag gtg tac acc ctg cct cct agc cag gaa gag atg acc aag     1104
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
        355                 360                 365
```

```
aac cag gtg tcc ctg acc tgt ctg gtg aag ggc ttc tac cct tcc gac     1152
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

atc gcc gtg gag tgg gag tcc aac ggc cag cct gag aac aac tac aag     1200
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

acc acc cct cct gtg ctg gac tcc gac ggc tcc ttc ttc ctg tac tcc     1248
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

agg ctg acc gtg gac aag tcc cgg tgg cag gag ggc aac gtc ttt tcc     1296
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
            420                 425                 430

tgc tcc gtg atg cac gag gcc ctg cac aac cac tac acc cag aag tcc     1344
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

ctg tcc ctg tct ctg ggc tga                                        1365
Leu Ser Leu Ser Leu Gly
    450
```

<210> 8
<211> 454
<212> PRT
<213> Homo sapiens

<400> 8

```
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                   10                  15

Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

Glu His Pro Ser Asp Gln Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

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

Met Leu Leu Pro Ser Gly Ser Leu Tyr Phe Leu Arg Ile Val His Gly
                85                  90                  95

Arg Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140
```

```
Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175

Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser
    210                 215                 220

Phe Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
        275                 280                 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    290                 295                 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
                325                 330                 335

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
        355                 360                 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415
```

```
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
            420                 425                 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445

Leu Ser Leu Ser Leu Gly
    450
```

<210> 9
<211> 1365
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1365)

<400> 9

```
atg att gcg gag ccc gct cac ttt tac ctg ttt gga tta ata tgt ctc       48
Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1               5                   10                  15

tgt tca ggc tcc cgt ctt cgt cag gaa gat ttt cca cct cgc att gtt       96
Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
            20                  25                  30

gaa cac cct tca gac ctg att gtc tca aaa gga gaa cct gca act ttg      144
Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
        35                  40                  45

aac tgc aaa gct gaa ggc cgc ccc aca ccc act att gaa tgg tac aaa      192
Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
    50                  55                  60

ggg gga gag aga gtg gag aca gac aaa gat gac cct cgc tca cac cga      240
Gly Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg
65                  70                  75                  80

atg ttg ctg ccg agt gga tct tta ttt ttc tta cgt ata gta cat gga      288
Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
                85                  90                  95

gcc gcc agt aga cct gat gaa gga gtc tat gtc tgt gta gca agg aat      336
Ala Ala Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn
            100                 105                 110

tac ctt gga gag gct gtg agc cac aat gca tcg ctg gaa gta gcc ata      384
Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
        115                 120                 125

ctt cgg gat gac ttc aga caa aac cct tcg gat gtc atg gtt gca gta      432
Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
    130                 135                 140

gga gag cct gca gta atg gaa tgc caa cct cca cga ggc cat cct gag      480
Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145                 150                 155                 160

ccc acc att tca tgg aag aaa gat ggc tct cca ctg gat gat aaa gat      528
Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
                165                 170                 175
```

```
gaa aga ata act ata cga gga gga aag ctc atg atc act tac acc cgt      576
Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
            180                 185                 190

aaa agt gac gct ggc aaa tat gtt tgt gtt ggt acc aat atg gtt ggg      624
Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
        195                 200                 205

gaa cgt gag agt gaa gta gcc gag ctg act gtc tta gag aga cca tca      672
Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser
    210                 215                 220

ttt gtg gag tcc aag tac ggc cct cct tgc cct ccc tgc cct gcc cct      720
Phe Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225                 230                 235                 240

gag ttc gag ggc gga cct agc gtg ttc ctg ttc cct cct aag cct aag      768
Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                245                 250                 255

gac acc ctg atg atc tcc cgg acc cct gag gtg acc tgt gtg gtg gtg      816
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
            260                 265                 270

gac gtg tcc cag gag gac cct gag gtc cag ttc aac tgg tac gtg gac      864
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
        275                 280                 285

ggc gtg gag gtg cac aac gcc aag acc aag cct cgg gag gag cag ttc      912
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
    290                 295                 300

aat tcc acc tac cgg gtg gtg tct gtg ctg acc gtg ctg cac cag gac      960
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305                 310                 315                 320

tgg ctg aac ggc aaa gaa tac aag tgt aag gtc tcc aac aag ggc ctg     1008
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
                325                 330                 335

ccc tcc tcc atc gag aaa acc atc tcc aag gcc aag ggc cag cct agg     1056
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
            340                 345                 350

gag cct cag gtg tac acc ctg cct cct agc cag gaa gag atg acc aag     1104
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
        355                 360                 365

aac cag gtg tcc ctg acc tgt ctg gtg aag ggc ttc tac cct tcc gac     1152
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
    370                 375                 380

atc gcc gtg gag tgg gag tcc aac ggc cag cct gag aac aac tac aag     1200
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385                 390                 395                 400

acc acc cct cct gtg ctg gac tcc gac ggc tcc ttc ttc ctg tac tcc     1248
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
                405                 410                 415

agg ctg acc gtg gac aag tcc cgg tgg cag gag ggc aac gtc ttt tcc     1296
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
            420                 425                 430

tgc tcc gtg atg cac gag gcc ctg cac aac cac tac acc cag aag tcc     1344
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
        435                 440                 445
```

ctg tcc ctg tct ctg ggc tga 1365
Leu Ser Leu Ser Leu Gly
450

<210> 10
<211> 454
<212> PRT
<213> Homo sapiens

<400> 10

Met Ile Ala Glu Pro Ala His Phe Tyr Leu Phe Gly Leu Ile Cys Leu
1 5 10 15

Cys Ser Gly Ser Arg Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val
20 25 30

Glu His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu
35 40 45

Asn Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys
50 55 60

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

Met Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly
85 90 95

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

Tyr Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile
115 120 125

Leu Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val
130 135 140

Gly Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu
145 150 155 160

Pro Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp
165 170 175

Glu Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg
180 185 190

Lys Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly
195 200 205

Glu Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser
210 215 220

Phe Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
225 230 235 240

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245 250 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
260 265 270

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
275 280 285

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
290 295 300

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
305 310 315 320

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
325 330 335

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
340 345 350

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
355 360 365

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
370 375 380

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
385 390 395 400

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
405 410 415

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
420 425 430

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
435 440 445

Leu Ser Leu Ser Leu Gly
450

<210> 11
<211> 717
<212> DNA
<213> Homo sapiens

<220>
<221> CDS

<222> (1)..(717)

<400> 11

```
atg tac agg atg caa ctc ctg tct tgc att gca cta agt ctt gca ctt       48
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                  10                  15

gtc acg aat tca ttg cac tgc cct gcc gcc tgt acc tgt agc aac aat       96
Val Thr Asn Ser Leu His Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn
            20                  25                  30

atc gta gac tgt cgt ggg aaa ggt ctc act gag atc ccc aca aat ctt      144
Ile Val Asp Cys Arg Gly Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu
        35                  40                  45

cca gag acc atc aca gaa ata cgt ttg gaa cag aac aca atc aaa gtc      192
Pro Glu Thr Ile Thr Glu Ile Arg Leu Glu Gln Asn Thr Ile Lys Val
    50                  55                  60

atc cct cct gga gct ttc tca cca tat aaa aag ctt aga cga att gac      240
Ile Pro Pro Gly Ala Phe Ser Pro Tyr Lys Lys Leu Arg Arg Ile Asp
65                  70                  75                  80

ctg agc aat aat cag atc tct gaa ctt gca cca gat gct ttc caa gga      288
Leu Ser Asn Asn Gln Ile Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly
                85                  90                  95

cta cgc tct ctg aat tca ctt gtc ctc tat gga aat aaa atc aca gaa      336
Leu Arg Ser Leu Asn Ser Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu
            100                 105                 110

ctc ccc aaa agt tta ttt gaa gga ctg ttt tcc tta cag ctc cta tta      384
Leu Pro Lys Ser Leu Phe Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu
        115                 120                 125

ttg aat gcc aac aag ata aac tgc ctt cgg gta gat gct ttt cag gat      432
Leu Asn Ala Asn Lys Ile Asn Cys Leu Arg Val Asp Ala Phe Gln Asp
    130                 135                 140

ctc cac aac ttg aac ctt ctc tcc cta tat gac aac aag ctt cag acc      480
Leu His Asn Leu Asn Leu Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr
145                 150                 155                 160

atc gcc aag ggg acc ttt tca cct ctt cgg gcc att caa act atg cat      528
Ile Ala Lys Gly Thr Phe Ser Pro Leu Arg Ala Ile Gln Thr Met His
                165                 170                 175

ttg gcc cag aac ccc ttt att tgt gac tgc cat ctc aag tgg cta gcg      576
Leu Ala Gln Asn Pro Phe Ile Cys Asp Cys His Leu Lys Trp Leu Ala
            180                 185                 190

gat tat ctc cat acc aac ccg att gag acc agt ggt gcc cgt tgc acc      624
Asp Tyr Leu His Thr Asn Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr
        195                 200                 205

agc ccc cgc cgc ctg gca aac aaa aga att gga cag atc aaa agc aag      672
Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys
    210                 215                 220

aaa ttc cgt tgt tca ggt agc gct cat cac cat cat cat cac tga          717
Lys Phe Arg Cys Ser Gly Ser Ala His His His His His His
225                 230                 235
```

<210> 12
<211> 238
<212> PRT
<213> Homo sapiens

<400> 12

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Leu His Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn
20 25 30

Ile Val Asp Cys Arg Gly Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu
35 40 45

Pro Glu Thr Ile Thr Glu Ile Arg Leu Glu Gln Asn Thr Ile Lys Val
50 55 60

Ile Pro Pro Gly Ala Phe Ser Pro Tyr Lys Lys Leu Arg Arg Ile Asp
65 70 75 80

Leu Ser Asn Asn Gln Ile Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly
85 90 95

Leu Arg Ser Leu Asn Ser Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu
100 105 110

Leu Pro Lys Ser Leu Phe Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu
115 120 125

Leu Asn Ala Asn Lys Ile Asn Cys Leu Arg Val Asp Ala Phe Gln Asp
130 135 140

Leu His Asn Leu Asn Leu Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr
145 150 155 160

Ile Ala Lys Gly Thr Phe Ser Pro Leu Arg Ala Ile Gln Thr Met His
165 170 175

Leu Ala Gln Asn Pro Phe Ile Cys Asp Cys His Leu Lys Trp Leu Ala
180 185 190

Asp Tyr Leu His Thr Asn Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr
195 200 205

Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys
210 215 220

Lys Phe Arg Cys Ser Gly Ser Ala His His His His His His
225 230 235

<210> 13
<211> 1467
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1467)

<400> 13

```
atg cgc ggc gtt ggc tgg cag atg ctg tcc ctg tcg ctg ggg tta gtg       48
Met Arg Gly Val Gly Trp Gln Met Leu Ser Leu Ser Leu Gly Leu Val
1               5                   10                  15

ctg gcg atc ctg aac aag gtg gca ccg cag gcg tgc ccg gcg cag tgc       96
Leu Ala Ile Leu Asn Lys Val Ala Pro Gln Ala Cys Pro Ala Gln Cys
            20                  25                  30

tct tgc tcg ggc agc aca gtg gac tgt cac ggg ctg gcg ctg cgc agc      144
Ser Cys Ser Gly Ser Thr Val Asp Cys His Gly Leu Ala Leu Arg Ser
        35                  40                  45

gtg ccc agg aat atc ccc cgc aac acc gag aga ctg gat tta aat gga      192
Val Pro Arg Asn Ile Pro Arg Asn Thr Glu Arg Leu Asp Leu Asn Gly
    50                  55                  60

aat aac atc aca aga att acg aag aca gat ttt gct ggt ctt aga cat      240
Asn Asn Ile Thr Arg Ile Thr Lys Thr Asp Phe Ala Gly Leu Arg His
65                  70                  75                  80

cta aga gtt ctt cag ctt atg gag aat aag att agc acc att gaa aga      288
Leu Arg Val Leu Gln Leu Met Glu Asn Lys Ile Ser Thr Ile Glu Arg
                85                  90                  95

gga gca ttc cag gat ctt aaa gaa cta gag aga ctg cgt tta aac aga      336
Gly Ala Phe Gln Asp Leu Lys Glu Leu Glu Arg Leu Arg Leu Asn Arg
            100                 105                 110

aat cac ctt cag ctg ttt cct gag ttg ctg ttt ctt ggg act gcg aag      384
Asn His Leu Gln Leu Phe Pro Glu Leu Leu Phe Leu Gly Thr Ala Lys
        115                 120                 125

cta tac agg ctt gat ctc agt gaa aac caa att cag gca atc cca agg      432
Leu Tyr Arg Leu Asp Leu Ser Glu Asn Gln Ile Gln Ala Ile Pro Arg
    130                 135                 140

aaa gct ttc cgt ggg gca gtt gac ata aaa aat ttg caa ctg gat tac      480
Lys Ala Phe Arg Gly Ala Val Asp Ile Lys Asn Leu Gln Leu Asp Tyr
145                 150                 155                 160

aac cag atc agc tgt att gaa gat ggg gca ttc agg gct ctc cgg gac      528
Asn Gln Ile Ser Cys Ile Glu Asp Gly Ala Phe Arg Ala Leu Arg Asp
                165                 170                 175

ctg gaa gtg ctc act ctc aac aat aac aac att act aga ctt tct gtg      576
Leu Glu Val Leu Thr Leu Asn Asn Asn Asn Ile Thr Arg Leu Ser Val
            180                 185                 190

gca agt ttc aac cat atg cct aaa ctt agg act ttt cga ctg cat tca      624
Ala Ser Phe Asn His Met Pro Lys Leu Arg Thr Phe Arg Leu His Ser
        195                 200                 205

aac aac ctg tat tgt gac tgc cac ctg gcc tgg ctc tcc gac tgg ctt      672
Asn Asn Leu Tyr Cys Asp Cys His Leu Ala Trp Leu Ser Asp Trp Leu
    210                 215                 220

cgc caa agg cct cgg gtt ggt ctg tac act cag tgt atg ggc ccc tcc      720
Arg Gln Arg Pro Arg Val Gly Leu Tyr Thr Gln Cys Met Gly Pro Ser
225                 230                 235                 240

cac ctg aga ggc cat aat gta gcc gag gtt caa aaa cga gaa ttt gtc      768
His Leu Arg Gly His Asn Val Ala Glu Val Gln Lys Arg Glu Phe Val
```

```
                245                 250                 255

tgc agt ggt cac cag tca ttt atg gct cct tct tgt agt gtt ttg cac      816
Cys Ser Gly His Gln Ser Phe Met Ala Pro Ser Cys Ser Val Leu His
            260                 265                 270

tgc cct gcc gcc tgt acc tgt agc aac aat atc gta gac tgt cgt ggg      864
Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn Ile Val Asp Cys Arg Gly
        275                 280                 285

aaa ggt ctc act gag atc ccc aca aat ctt cca gag acc atc aca gaa      912
Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu Pro Glu Thr Ile Thr Glu
    290                 295                 300

ata cgt ttg gaa cag aac aca atc aaa gtc atc cct cct gga gct ttc      960
Ile Arg Leu Glu Gln Asn Thr Ile Lys Val Ile Pro Pro Gly Ala Phe
305                 310                 315                 320

tca cca tat aaa aag ctt aga cga att gac ctg agc aat aat cag atc     1008
Ser Pro Tyr Lys Lys Leu Arg Arg Ile Asp Leu Ser Asn Asn Gln Ile
                325                 330                 335

tct gaa ctt gca cca gat gct ttc caa gga cta cgc tct ctg aat tca     1056
Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly Leu Arg Ser Leu Asn Ser
            340                 345                 350

ctt gtc ctc tat gga aat aaa atc aca gaa ctc ccc aaa agt tta ttt     1104
Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu Leu Pro Lys Ser Leu Phe
        355                 360                 365

gaa gga ctg ttt tcc tta cag ctc cta tta ttg aat gcc aac aag ata     1152
Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu Leu Asn Ala Asn Lys Ile
    370                 375                 380

aac tgc ctt cgg gta gat gct ttt cag gat ctc cac aac ttg aac ctt     1200
Asn Cys Leu Arg Val Asp Ala Phe Gln Asp Leu His Asn Leu Asn Leu
385                 390                 395                 400

ctc tcc cta tat gac aac aag ctt cag acc atc gcc aag ggg acc ttt     1248
Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr Ile Ala Lys Gly Thr Phe
                405                 410                 415

tca cct ctt cgg gcc att caa act atg cat ttg gcc cag aac ccc ttt     1296
Ser Pro Leu Arg Ala Ile Gln Thr Met His Leu Ala Gln Asn Pro Phe
            420                 425                 430

att tgt gac tgc cat ctc aag tgg cta gcg gat tat ctc cat acc aac     1344
Ile Cys Asp Cys His Leu Lys Trp Leu Ala Asp Tyr Leu His Thr Asn
        435                 440                 445

ccg att gag acc agt ggt gcc cgt tgc acc agc ccc cgc cgc ctg gca     1392
Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr Ser Pro Arg Arg Leu Ala
    450                 455                 460

aac aaa aga att gga cag atc aaa agc aag aaa ttc cgt tgt tca ggt     1440
Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys Lys Phe Arg Cys Ser Gly
465                 470                 475                 480

agc gct cat cac cat cat cat cac tga                                1467
Ser Ala His His His His His His
                485
```

<210> 14
<211> 488
<212> PRT
<213> Homo sapiens

<400> 14

```
Met Arg Gly Val Gly Trp Gln Met Leu Ser Leu Ser Leu Gly Leu Val
1               5                  10                  15

Leu Ala Ile Leu Asn Lys Val Ala Pro Gln Ala Cys Pro Ala Gln Cys
            20                  25                  30

Ser Cys Ser Gly Ser Thr Val Asp Cys His Gly Leu Ala Leu Arg Ser
        35                  40                  45

Val Pro Arg Asn Ile Pro Arg Asn Thr Glu Arg Leu Asp Leu Asn Gly
    50                  55                  60

Asn Asn Ile Thr Arg Ile Thr Lys Thr Asp Phe Ala Gly Leu Arg His
65                  70                  75                  80

Leu Arg Val Leu Gln Leu Met Glu Asn Lys Ile Ser Thr Ile Glu Arg
                85                  90                  95

Gly Ala Phe Gln Asp Leu Lys Glu Leu Glu Arg Leu Arg Leu Asn Arg
            100                 105                 110

Asn His Leu Gln Leu Phe Pro Glu Leu Leu Phe Leu Gly Thr Ala Lys
        115                 120                 125

Leu Tyr Arg Leu Asp Leu Ser Glu Asn Gln Ile Gln Ala Ile Pro Arg
    130                 135                 140

Lys Ala Phe Arg Gly Ala Val Asp Ile Lys Asn Leu Gln Leu Asp Tyr
145                 150                 155                 160

Asn Gln Ile Ser Cys Ile Glu Asp Gly Ala Phe Arg Ala Leu Arg Asp
                165                 170                 175

Leu Glu Val Leu Thr Leu Asn Asn Asn Asn Ile Thr Arg Leu Ser Val
            180                 185                 190

Ala Ser Phe Asn His Met Pro Lys Leu Arg Thr Phe Arg Leu His Ser
        195                 200                 205

Asn Asn Leu Tyr Cys Asp Cys His Leu Ala Trp Leu Ser Asp Trp Leu
    210                 215                 220

Arg Gln Arg Pro Arg Val Gly Leu Tyr Thr Gln Cys Met Gly Pro Ser
225                 230                 235                 240

His Leu Arg Gly His Asn Val Ala Glu Val Gln Lys Arg Glu Phe Val
                245                 250                 255

Cys Ser Gly His Gln Ser Phe Met Ala Pro Ser Cys Ser Val Leu His
            260                 265                 270
```

```
Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn Ile Val Asp Cys Arg Gly
        275                 280                 285

Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu Pro Glu Thr Ile Thr Glu
    290                 295                 300

Ile Arg Leu Glu Gln Asn Thr Ile Lys Val Ile Pro Pro Gly Ala Phe
305                 310                 315                 320

Ser Pro Tyr Lys Lys Leu Arg Arg Ile Asp Leu Ser Asn Asn Gln Ile
                325                 330                 335

Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly Leu Arg Ser Leu Asn Ser
            340                 345                 350

Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu Leu Pro Lys Ser Leu Phe
        355                 360                 365

Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu Leu Asn Ala Asn Lys Ile
    370                 375                 380

Asn Cys Leu Arg Val Asp Ala Phe Gln Asp Leu His Asn Leu Asn Leu
385                 390                 395                 400

Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr Ile Ala Lys Gly Thr Phe
                405                 410                 415

Ser Pro Leu Arg Ala Ile Gln Thr Met His Leu Ala Gln Asn Pro Phe
            420                 425                 430

Ile Cys Asp Cys His Leu Lys Trp Leu Ala Asp Tyr Leu His Thr Asn
        435                 440                 445

Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr Ser Pro Arg Arg Leu Ala
    450                 455                 460

Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys Lys Phe Arg Cys Ser Gly
465                 470                 475                 480

Ser Ala His His His His His His
                485
```

<210> 15
<211> 3390
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(3390)

<400> 15

```
atg cgc ggc gtt ggc tgg cag atg ctg tcc ctg tcg ctg ggg tta gtg       48
Met Arg Gly Val Gly Trp Gln Met Leu Ser Leu Ser Leu Gly Leu Val
1               5                  10                  15

ctg gcg atc ctg aac aag gtg gca ccg cag gcg tgc ccg gcg cag tgc       96
Leu Ala Ile Leu Asn Lys Val Ala Pro Gln Ala Cys Pro Ala Gln Cys
            20                  25                  30

tct tgc tcg ggc agc aca gtg gac tgt cac ggg ctg gcg ctg cgc agc      144
Ser Cys Ser Gly Ser Thr Val Asp Cys His Gly Leu Ala Leu Arg Ser
        35                  40                  45

gtg ccc agg aat atc ccc cgc aac acc gag aga ctg gat tta aat gga      192
Val Pro Arg Asn Ile Pro Arg Asn Thr Glu Arg Leu Asp Leu Asn Gly
    50                  55                  60

aat aac atc aca aga att acg aag aca gat ttt gct ggt ctt aga cat      240
Asn Asn Ile Thr Arg Ile Thr Lys Thr Asp Phe Ala Gly Leu Arg His
65                  70                  75                  80

cta aga gtt ctt cag ctt atg gag aat aag att agc acc att gaa aga      288
Leu Arg Val Leu Gln Leu Met Glu Asn Lys Ile Ser Thr Ile Glu Arg
                85                  90                  95

gga gca ttc cag gat ctt aaa gaa cta gag aga ctg cgt tta aac aga      336
Gly Ala Phe Gln Asp Leu Lys Glu Leu Glu Arg Leu Arg Leu Asn Arg
            100                 105                 110

aat cac ctt cag ctg ttt cct gag ttg ctg ttt ctt ggg act gcg aag      384
Asn His Leu Gln Leu Phe Pro Glu Leu Leu Phe Leu Gly Thr Ala Lys
        115                 120                 125

cta tac agg ctt gat ctc agt gaa aac caa att cag gca atc cca agg      432
Leu Tyr Arg Leu Asp Leu Ser Glu Asn Gln Ile Gln Ala Ile Pro Arg
    130                 135                 140

aaa gct ttc cgt ggg gca gtt gac ata aaa aat ttg caa ctg gat tac      480
Lys Ala Phe Arg Gly Ala Val Asp Ile Lys Asn Leu Gln Leu Asp Tyr
145                 150                 155                 160

aac cag atc agc tgt att gaa gat ggg gca ttc agg gct ctc cgg gac      528
Asn Gln Ile Ser Cys Ile Glu Asp Gly Ala Phe Arg Ala Leu Arg Asp
                165                 170                 175

ctg gaa gtg ctc act ctc aac aat aac aac att act aga ctt tct gtg      576
Leu Glu Val Leu Thr Leu Asn Asn Asn Asn Ile Thr Arg Leu Ser Val
            180                 185                 190

gca agt ttc aac cat atg cct aaa ctt agg act ttt cga ctg cat tca      624
Ala Ser Phe Asn His Met Pro Lys Leu Arg Thr Phe Arg Leu His Ser
        195                 200                 205

aac aac ctg tat tgt gac tgc cac ctg gcc tgg ctc tcc gac tgg ctt      672
Asn Asn Leu Tyr Cys Asp Cys His Leu Ala Trp Leu Ser Asp Trp Leu
    210                 215                 220

cgc caa agg cct cgg gtt ggt ctg tac act cag tgt atg ggc ccc tcc      720
Arg Gln Arg Pro Arg Val Gly Leu Tyr Thr Gln Cys Met Gly Pro Ser
225                 230                 235                 240

cac ctg aga ggc cat aat gta gcc gag gtt caa aaa cga gaa ttt gtc      768
His Leu Arg Gly His Asn Val Ala Glu Val Gln Lys Arg Glu Phe Val
                245                 250                 255

tgc agt ggt cac cag tca ttt atg gct cct tct tgt agt gtt ttg cac      816
Cys Ser Gly His Gln Ser Phe Met Ala Pro Ser Cys Ser Val Leu His
            260                 265                 270
```

```
tgc cct gcc gcc tgt acc tgt agc aac aat atc gta gac tgt cgt ggg      864
Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn Ile Val Asp Cys Arg Gly
        275                 280                 285

aaa ggt ctc act gag atc ccc aca aat ctt cca gag acc atc aca gaa      912
Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu Pro Glu Thr Ile Thr Glu
    290                 295                 300

ata cgt ttg gaa cag aac aca atc aaa gtc atc cct cct gga gct ttc      960
Ile Arg Leu Glu Gln Asn Thr Ile Lys Val Ile Pro Pro Gly Ala Phe
305                 310                 315                 320

tca cca tat aaa aag ctt aga cga att gac ctg agc aat aat cag atc     1008
Ser Pro Tyr Lys Lys Leu Arg Arg Ile Asp Leu Ser Asn Asn Gln Ile
                325                 330                 335

tct gaa ctt gca cca gat gct ttc caa gga cta cgc tct ctg aat tca     1056
Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly Leu Arg Ser Leu Asn Ser
            340                 345                 350

ctt gtc ctc tat gga aat aaa atc aca gaa ctc ccc aaa agt tta ttt     1104
Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu Leu Pro Lys Ser Leu Phe
        355                 360                 365

gaa gga ctg ttt tcc tta cag ctc cta tta ttg aat gcc aac aag ata     1152
Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu Leu Asn Ala Asn Lys Ile
    370                 375                 380

aac tgc ctt cgg gta gat gct ttt cag gat ctc cac aac ttg aac ctt     1200
Asn Cys Leu Arg Val Asp Ala Phe Gln Asp Leu His Asn Leu Asn Leu
385                 390                 395                 400

ctc tcc cta tat gac aac aag ctt cag acc atc gcc aag ggg acc ttt     1248
Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr Ile Ala Lys Gly Thr Phe
                405                 410                 415

tca cct ctt cgg gcc att caa act atg cat ttg gcc cag aac ccc ttt     1296
Ser Pro Leu Arg Ala Ile Gln Thr Met His Leu Ala Gln Asn Pro Phe
            420                 425                 430

att tgt gac tgc cat ctc aag tgg cta gcg gat tat ctc cat acc aac     1344
Ile Cys Asp Cys His Leu Lys Trp Leu Ala Asp Tyr Leu His Thr Asn
        435                 440                 445

ccg att gag acc agt ggt gcc cgt tgc acc agc ccc cgc cgc ctg gca     1392
Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr Ser Pro Arg Arg Leu Ala
    450                 455                 460

aac aaa aga att gga cag atc aaa agc aag aaa ttc cgt tgt tca gct     1440
Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys Lys Phe Arg Cys Ser Ala
465                 470                 475                 480

aaa gaa cag tat ttc att cca ggt aca gaa gat tat cga tca aaa tta     1488
Lys Glu Gln Tyr Phe Ile Pro Gly Thr Glu Asp Tyr Arg Ser Lys Leu
                485                 490                 495

agt gga gac tgc ttt gcg gat ctg gct tgc cct gaa aag tgt cgc tgt     1536
Ser Gly Asp Cys Phe Ala Asp Leu Ala Cys Pro Glu Lys Cys Arg Cys
            500                 505                 510

gaa gga acc aca gta gat tgc tct aat caa aag ctc aac aaa atc ccg     1584
Glu Gly Thr Thr Val Asp Cys Ser Asn Gln Lys Leu Asn Lys Ile Pro
        515                 520                 525

gag cac att ccc cag tac act gca gag ttg cgt ctc aat aat aat gaa     1632
Glu His Ile Pro Gln Tyr Thr Ala Glu Leu Arg Leu Asn Asn Asn Glu
    530                 535                 540
```

```
ttt acc gtg ttg gaa gcc aca gga atc ttt aag aaa ctt cct caa tta      1680
Phe Thr Val Leu Glu Ala Thr Gly Ile Phe Lys Lys Leu Pro Gln Leu
545                 550                 555                 560

cgt aaa ata aac ttt agc aac aat aag atc aca gat att gag gag gga      1728
Arg Lys Ile Asn Phe Ser Asn Asn Lys Ile Thr Asp Ile Glu Glu Gly
                565                 570                 575

gca ttt gaa gga gca tct ggt gta aat gaa ata ctt ctt acg agt aat      1776
Ala Phe Glu Gly Ala Ser Gly Val Asn Glu Ile Leu Leu Thr Ser Asn
            580                 585                 590

cgt ttg gaa aat gtg cag cat aag atg ttc aag gga ttg gaa agc ctc      1824
Arg Leu Glu Asn Val Gln His Lys Met Phe Lys Gly Leu Glu Ser Leu
        595                 600                 605

aaa act ttg atg ttg aga agc aat cga ata acc tgt gtg ggg aat gac      1872
Lys Thr Leu Met Leu Arg Ser Asn Arg Ile Thr Cys Val Gly Asn Asp
    610                 615                 620

agt ttc ata gga ctc agt tct gtg cgt ttg ctt tct ttg tat gat aat      1920
Ser Phe Ile Gly Leu Ser Ser Val Arg Leu Leu Ser Leu Tyr Asp Asn
625                 630                 635                 640

caa att act aca gtt gca cca ggg gca ttt gat act ctc cat tct tta      1968
Gln Ile Thr Thr Val Ala Pro Gly Ala Phe Asp Thr Leu His Ser Leu
                645                 650                 655

tct act cta aac ctc ttg gcc aat cct ttt aac tgt aac tgc tac ctg      2016
Ser Thr Leu Asn Leu Leu Ala Asn Pro Phe Asn Cys Asn Cys Tyr Leu
            660                 665                 670

gct tgg ttg gga gag tgg ctg aga aag aag aga att gtc acg gga aat      2064
Ala Trp Leu Gly Glu Trp Leu Arg Lys Lys Arg Ile Val Thr Gly Asn
        675                 680                 685

cct aga tgt caa aaa cca tac ttc ctg aaa gaa ata ccc atc cag gat      2112
Pro Arg Cys Gln Lys Pro Tyr Phe Leu Lys Glu Ile Pro Ile Gln Asp
    690                 695                 700

gtg gcc att cag gac ttc act tgt gat gac gga aat gat gac aat agt      2160
Val Ala Ile Gln Asp Phe Thr Cys Asp Asp Gly Asn Asp Asp Asn Ser
705                 710                 715                 720

tgc tcc cca ctt tct cgc tgt cct act gaa tgt act tgc ttg gat aca      2208
Cys Ser Pro Leu Ser Arg Cys Pro Thr Glu Cys Thr Cys Leu Asp Thr
                725                 730                 735

gtc gtc cga tgt agc aac aag ggt ttg aag gtc ttg ccg aaa ggt att      2256
Val Val Arg Cys Ser Asn Lys Gly Leu Lys Val Leu Pro Lys Gly Ile
            740                 745                 750

cca aga gat gtc aca gag ttg tat ctg gat gga aac caa ttt aca ctg      2304
Pro Arg Asp Val Thr Glu Leu Tyr Leu Asp Gly Asn Gln Phe Thr Leu
        755                 760                 765

gtt ccc aag gaa ctc tcc aac tac aaa cat tta aca ctt ata gac tta      2352
Val Pro Lys Glu Leu Ser Asn Tyr Lys His Leu Thr Leu Ile Asp Leu
    770                 775                 780

agt aac aac aga ata agc acg ctt tct aat cag agc ttc agc aac atg      2400
Ser Asn Asn Arg Ile Ser Thr Leu Ser Asn Gln Ser Phe Ser Asn Met
785                 790                 795                 800

acc cag ctc ctc acc tta att ctt agt tac aac cgt ctg aga tgt att      2448
Thr Gln Leu Leu Thr Leu Ile Leu Ser Tyr Asn Arg Leu Arg Cys Ile
                805                 810                 815
```

```
cct cct cgc acc ttt gat gga tta aag tct ctt cga tta ctt tct cta     2496
Pro Pro Arg Thr Phe Asp Gly Leu Lys Ser Leu Arg Leu Leu Ser Leu
            820                 825                 830

cat gga aat gac att tct gtt gtg cct gaa ggt gct ttc aat gat ctt     2544
His Gly Asn Asp Ile Ser Val Val Pro Glu Gly Ala Phe Asn Asp Leu
        835                 840                 845

tct gca tta tca cat cta gca att gga gcc aac cct ctt tac tgt gat     2592
Ser Ala Leu Ser His Leu Ala Ile Gly Ala Asn Pro Leu Tyr Cys Asp
    850                 855                 860

tgt aac atg cag tgg tta tcc gac tgg gtg aag tcg gaa tat aag gag     2640
Cys Asn Met Gln Trp Leu Ser Asp Trp Val Lys Ser Glu Tyr Lys Glu
865                 870                 875                 880

cct gga att gct cgt tgt gct ggt cct gga gaa atg gca gat aaa ctt     2688
Pro Gly Ile Ala Arg Cys Ala Gly Pro Gly Glu Met Ala Asp Lys Leu
                885                 890                 895

tta ctc aca act ccc tcc aaa aaa ttt acc tgt caa ggt cct gtg gat     2736
Leu Leu Thr Thr Pro Ser Lys Lys Phe Thr Cys Gln Gly Pro Val Asp
            900                 905                 910

gtc aat att cta gct aag tgt aac ccc tgc cta tca aat ccg tgt aaa     2784
Val Asn Ile Leu Ala Lys Cys Asn Pro Cys Leu Ser Asn Pro Cys Lys
        915                 920                 925

aat gat ggc aca tgt aat agt gat cca gtt gac ttt tac cga tgc acc     2832
Asn Asp Gly Thr Cys Asn Ser Asp Pro Val Asp Phe Tyr Arg Cys Thr
    930                 935                 940

tgt cca tat ggt ttc aag ggg cag gac tgt gat gtc cca att cat gcc     2880
Cys Pro Tyr Gly Phe Lys Gly Gln Asp Cys Asp Val Pro Ile His Ala
945                 950                 955                 960

tgc atc agt aac cca tgt aaa cat gga gga act tgc cac tta aag gaa     2928
Cys Ile Ser Asn Pro Cys Lys His Gly Gly Thr Cys His Leu Lys Glu
                965                 970                 975

gga gaa gaa gat gga ttc tgg tgt att tgt gct gat gga ttt gaa gga     2976
Gly Glu Glu Asp Gly Phe Trp Cys Ile Cys Ala Asp Gly Phe Glu Gly
            980                 985                 990

gaa aat tgt gaa gtc aac gtt gat  gat tgt gaa gat aat  gac tgt gaa   3024
Glu Asn Cys Glu Val Asn Val Asp  Asp Cys Glu Asp Asn  Asp Cys Glu
        995                 1000                1005

aat aat  tct aca tgt gtc gat  ggc att aat aac tac  aca tgc ctt      3069
Asn Asn  Ser Thr Cys Val Asp  Gly Ile Asn Asn Tyr  Thr Cys Leu
    1010                1015                1020

tgc cca  cct gag tat aca ggt  gag ttg tgt gag gag  aag ctg gac      3114
Cys Pro  Pro Glu Tyr Thr Gly  Glu Leu Cys Glu Glu  Lys Leu Asp
    1025                1030                1035

ttc tgt  gcc cag gac ctg aac  ccc tgc cag cac gat  tca aag tgc      3159
Phe Cys  Ala Gln Asp Leu Asn  Pro Cys Gln His Asp  Ser Lys Cys
    1040                1045                1050

atc cta  act cca aag gga ttc  aaa tgt gac tgc aca  cca ggg tac      3204
Ile Leu  Thr Pro Lys Gly Phe  Lys Cys Asp Cys Thr  Pro Gly Tyr
    1055                1060                1065

gta ggt  gaa cac tgc gac atc  gat ttt gac gac tgc  caa gac aac      3249
Val Gly  Glu His Cys Asp Ile  Asp Phe Asp Asp Cys  Gln Asp Asn
    1070                1075                1080
```

```
aag tgt  aaa aac gga gcc cac  tgc aca gat gca gtg  aac ggc tat      3294
Lys Cys  Lys Asn Gly Ala His  Cys Thr Asp Ala Val  Asn Gly Tyr
    1085                 1090                 1095

acg tgc  ata tgc ccc gaa ggt  tac agt ggc ttg ttc  tgt gag ttt      3339
Thr Cys  Ile Cys Pro Glu Gly  Tyr Ser Gly Leu Phe  Cys Glu Phe
    1100                 1105                 1110

tct cca  ccc atg gtc ctc cct  cgt agc gct cat cac  cat cat cat      3384
Ser Pro  Pro Met Val Leu Pro  Arg Ser Ala His His  His His His
    1115                 1120                 1125

cac tga                                                          3390
His
```

<210> 16
<211> 1129
<212> PRT
<213> Homo sapiens

<400> 16

```
Met Arg Gly Val Gly Trp Gln Met Leu Ser Leu Ser Leu Gly Leu Val
1               5                  10                  15

Leu Ala Ile Leu Asn Lys Val Ala Pro Gln Ala Cys Pro Ala Gln Cys
            20                  25                  30

Ser Cys Ser Gly Ser Thr Val Asp Cys His Gly Leu Ala Leu Arg Ser
        35                  40                  45

Val Pro Arg Asn Ile Pro Arg Asn Thr Glu Arg Leu Asp Leu Asn Gly
    50                  55                  60

Asn Asn Ile Thr Arg Ile Thr Lys Thr Asp Phe Ala Gly Leu Arg His
65                  70                  75                  80

Leu Arg Val Leu Gln Leu Met Glu Asn Lys Ile Ser Thr Ile Glu Arg
                85                  90                  95

Gly Ala Phe Gln Asp Leu Lys Glu Leu Glu Arg Leu Arg Leu Asn Arg
            100                 105                 110

Asn His Leu Gln Leu Phe Pro Glu Leu Leu Phe Leu Gly Thr Ala Lys
        115                 120                 125

Leu Tyr Arg Leu Asp Leu Ser Glu Asn Gln Ile Gln Ala Ile Pro Arg
    130                 135                 140

Lys Ala Phe Arg Gly Ala Val Asp Ile Lys Asn Leu Gln Leu Asp Tyr
145                 150                 155                 160

Asn Gln Ile Ser Cys Ile Glu Asp Gly Ala Phe Arg Ala Leu Arg Asp
                165                 170                 175
```

Leu Glu Val Leu Thr Leu Asn Asn Asn Asn Ile Thr Arg Leu Ser Val
180 185 190

Ala Ser Phe Asn His Met Pro Lys Leu Arg Thr Phe Arg Leu His Ser
195 200 205

Asn Asn Leu Tyr Cys Asp Cys His Leu Ala Trp Leu Ser Asp Trp Leu
210 215 220

Arg Gln Arg Pro Arg Val Gly Leu Tyr Thr Gln Cys Met Gly Pro Ser
225 230 235 240

His Leu Arg Gly His Asn Val Ala Glu Val Gln Lys Arg Glu Phe Val
245 250 255

Cys Ser Gly His Gln Ser Phe Met Ala Pro Ser Cys Ser Val Leu His
260 265 270

Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn Ile Val Asp Cys Arg Gly
275 280 285

Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu Pro Glu Thr Ile Thr Glu
290 295 300

Ile Arg Leu Glu Gln Asn Thr Ile Lys Val Ile Pro Pro Gly Ala Phe
305 310 315 320

Ser Pro Tyr Lys Lys Leu Arg Arg Ile Asp Leu Ser Asn Asn Gln Ile
325 330 335

Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly Leu Arg Ser Leu Asn Ser
340 345 350

Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu Leu Pro Lys Ser Leu Phe
355 360 365

Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu Leu Asn Ala Asn Lys Ile
370 375 380

Asn Cys Leu Arg Val Asp Ala Phe Gln Asp Leu His Asn Leu Asn Leu
385 390 395 400

Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr Ile Ala Lys Gly Thr Phe
405 410 415

Ser Pro Leu Arg Ala Ile Gln Thr Met His Leu Ala Gln Asn Pro Phe
420 425 430

Ile Cys Asp Cys His Leu Lys Trp Leu Ala Asp Tyr Leu His Thr Asn
435 440 445

```
Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr Ser Pro Arg Arg Leu Ala
    450                 455                 460

Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys Lys Phe Arg Cys Ser Ala
465                 470                 475                 480

Lys Glu Gln Tyr Phe Ile Pro Gly Thr Glu Asp Tyr Arg Ser Lys Leu
                485                 490                 495

Ser Gly Asp Cys Phe Ala Asp Leu Ala Cys Pro Glu Lys Cys Arg Cys
            500                 505                 510

Glu Gly Thr Thr Val Asp Cys Ser Asn Gln Lys Leu Asn Lys Ile Pro
        515                 520                 525

Glu His Ile Pro Gln Tyr Thr Ala Glu Leu Arg Leu Asn Asn Asn Glu
    530                 535                 540

Phe Thr Val Leu Glu Ala Thr Gly Ile Phe Lys Lys Leu Pro Gln Leu
545                 550                 555                 560

Arg Lys Ile Asn Phe Ser Asn Asn Lys Ile Thr Asp Ile Glu Glu Gly
                565                 570                 575

Ala Phe Glu Gly Ala Ser Gly Val Asn Glu Ile Leu Leu Thr Ser Asn
            580                 585                 590

Arg Leu Glu Asn Val Gln His Lys Met Phe Lys Gly Leu Glu Ser Leu
        595                 600                 605

Lys Thr Leu Met Leu Arg Ser Asn Arg Ile Thr Cys Val Gly Asn Asp
    610                 615                 620

Ser Phe Ile Gly Leu Ser Ser Val Arg Leu Leu Ser Leu Tyr Asp Asn
625                 630                 635                 640

Gln Ile Thr Thr Val Ala Pro Gly Ala Phe Asp Thr Leu His Ser Leu
                645                 650                 655

Ser Thr Leu Asn Leu Leu Ala Asn Pro Phe Asn Cys Asn Cys Tyr Leu
            660                 665                 670

Ala Trp Leu Gly Glu Trp Leu Arg Lys Lys Arg Ile Val Thr Gly Asn
        675                 680                 685

Pro Arg Cys Gln Lys Pro Tyr Phe Leu Lys Glu Ile Pro Ile Gln Asp
    690                 695                 700

Val Ala Ile Gln Asp Phe Thr Cys Asp Asp Gly Asn Asp Asp Asn Ser
705                 710                 715                 720
```

```
Cys Ser Pro Leu Ser Arg Cys Pro Thr Glu Cys Thr Cys Leu Asp Thr
                725                 730                 735

Val Val Arg Cys Ser Asn Lys Gly Leu Lys Val Leu Pro Lys Gly Ile
            740                 745                 750

Pro Arg Asp Val Thr Glu Leu Tyr Leu Asp Gly Asn Gln Phe Thr Leu
        755                 760                 765

Val Pro Lys Glu Leu Ser Asn Tyr Lys His Leu Thr Leu Ile Asp Leu
    770                 775                 780

Ser Asn Asn Arg Ile Ser Thr Leu Ser Asn Gln Ser Phe Ser Asn Met
785                 790                 795                 800

Thr Gln Leu Leu Thr Leu Ile Leu Ser Tyr Asn Arg Leu Arg Cys Ile
                805                 810                 815

Pro Pro Arg Thr Phe Asp Gly Leu Lys Ser Leu Arg Leu Leu Ser Leu
            820                 825                 830

His Gly Asn Asp Ile Ser Val Val Pro Glu Gly Ala Phe Asn Asp Leu
        835                 840                 845

Ser Ala Leu Ser His Leu Ala Ile Gly Ala Asn Pro Leu Tyr Cys Asp
    850                 855                 860

Cys Asn Met Gln Trp Leu Ser Asp Trp Val Lys Ser Glu Tyr Lys Glu
865                 870                 875                 880

Pro Gly Ile Ala Arg Cys Ala Gly Pro Gly Glu Met Ala Asp Lys Leu
                885                 890                 895

Leu Leu Thr Thr Pro Ser Lys Lys Phe Thr Cys Gln Gly Pro Val Asp
            900                 905                 910

Val Asn Ile Leu Ala Lys Cys Asn Pro Cys Leu Ser Asn Pro Cys Lys
        915                 920                 925

Asn Asp Gly Thr Cys Asn Ser Asp Pro Val Asp Phe Tyr Arg Cys Thr
    930                 935                 940

Cys Pro Tyr Gly Phe Lys Gly Gln Asp Cys Asp Val Pro Ile His Ala
945                 950                 955                 960

Cys Ile Ser Asn Pro Cys Lys His Gly Gly Thr Cys His Leu Lys Glu
                965                 970                 975

Gly Glu Glu Asp Gly Phe Trp Cys Ile Cys Ala Asp Gly Phe Glu Gly
            980                 985                 990
```

```
Glu Asn Cys Glu Val Asn Val Asp  Asp Cys Glu Asp Asn  Asp Cys Glu
        995                 1000                1005

Asn Asn  Ser Thr Cys Val Asp  Gly Ile Asn Asn Tyr  Thr Cys Leu
    1010                1015                1020

Cys Pro  Pro Glu Tyr Thr Gly  Glu Leu Cys Glu Glu  Lys Leu Asp
    1025                1030                1035

Phe Cys  Ala Gln Asp Leu Asn  Pro Cys Gln His Asp  Ser Lys Cys
    1040                1045                1050

Ile Leu  Thr Pro Lys Gly Phe  Lys Cys Asp Cys Thr  Pro Gly Tyr
    1055                1060                1065

Val Gly  Glu His Cys Asp Ile  Asp Phe Asp Asp Cys  Gln Asp Asn
    1070                1075                1080

Lys Cys  Lys Asn Gly Ala His  Cys Thr Asp Ala Val  Asn Gly Tyr
    1085                1090                1095

Thr Cys  Ile Cys Pro Glu Gly  Tyr Ser Gly Leu Phe  Cys Glu Phe
    1100                1105                1110

Ser Pro  Pro Met Val Leu Pro  Arg Ser Ala His His  His His His
    1115                1120                1125

His
```

<210> 17
<211> 717
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)..(717)

<400> 17

```
atg tac agg atg caa ctc ctg tct tgc att gca cta agt ctt gca ctt       48
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                  10                  15

gtc acg aat tca ttg cac tgc cct gcc gcc tgt acc tgt agc aac aat       96
Val Thr Asn Ser Leu His Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn
            20                  25                  30

atc gta gac tgt cgt ggg aaa ggt ctc act gag atc ccc aca aat ctt      144
Ile Val Asp Cys Arg Gly Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu
        35                  40                  45

cca gag acc atc aca gaa ata cgt ttg gaa cag aac agc atc aga gtc      192
Pro Glu Thr Ile Thr Glu Ile Arg Leu Glu Gln Asn Ser Ile Arg Val
    50                  55                  60
```

```
atc cct cct gga gct ttc tca cca tat aaa aag ctt aga cga ctg gac      240
Ile Pro Pro Gly Ala Phe Ser Pro Tyr Lys Lys Leu Arg Arg Leu Asp
65                  70                  75                  80

ctg agc aat aat cag atc tct gaa ctt gca cca gat gct ttc caa gga      288
Leu Ser Asn Asn Gln Ile Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly
                85                  90                  95

cta cgc tct ctg aat tca ctt gtc ctc tat gga aat aaa atc aca gaa      336
Leu Arg Ser Leu Asn Ser Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu
            100                 105                 110

ctc ccc aaa agt tta ttt gaa gga ctg ttt tcc tta cag ctc cta tta      384
Leu Pro Lys Ser Leu Phe Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu
        115                 120                 125

ttg aat gcc aac aag ata aac tgc ctt cgg gta gat gct ttt cag gat      432
Leu Asn Ala Asn Lys Ile Asn Cys Leu Arg Val Asp Ala Phe Gln Asp
    130                 135                 140

ctc cac aac ttg aac ctt ctc tcc cta tat gac aac aag ctt cag acc      480
Leu His Asn Leu Asn Leu Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr
145                 150                 155                 160

gtc gcc aag ggg acc ttt tca gct ctt cgg gcc att caa act atg cat      528
Val Ala Lys Gly Thr Phe Ser Ala Leu Arg Ala Ile Gln Thr Met His
                165                 170                 175

ttg gcc cag aac ccc ttt att tgt gac tgc cat ctc aag tgg cta gcg      576
Leu Ala Gln Asn Pro Phe Ile Cys Asp Cys His Leu Lys Trp Leu Ala
            180                 185                 190

gat tat ctc cat acc aac ccg att gag acc agt ggt gcc cgt tgc acc      624
Asp Tyr Leu His Thr Asn Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr
        195                 200                 205

agc ccc cgc cgc ctg gca aac aaa aga att gga cag atc aaa agc aag      672
Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys
    210                 215                 220

aaa ttc cgt tgt tca ggt agc gct cat cac cat cat cat cac tga          717
Lys Phe Arg Cys Ser Gly Ser Ala His His His His His His
225                 230                 235
```

<210> 18
<211> 238
<212> PRT
<213> Mus musculus

<400> 18

```
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Leu His Cys Pro Ala Ala Cys Thr Cys Ser Asn Asn
            20                  25                  30

Ile Val Asp Cys Arg Gly Lys Gly Leu Thr Glu Ile Pro Thr Asn Leu
        35                  40                  45

Pro Glu Thr Ile Thr Glu Ile Arg Leu Glu Gln Asn Ser Ile Arg Val
    50                  55                  60
```

```
Ile Pro Pro Gly Ala Phe Ser Pro Tyr Lys Lys Leu Arg Arg Leu Asp
65                  70                  75                  80

Leu Ser Asn Asn Gln Ile Ser Glu Leu Ala Pro Asp Ala Phe Gln Gly
                85                  90                  95

Leu Arg Ser Leu Asn Ser Leu Val Leu Tyr Gly Asn Lys Ile Thr Glu
            100                 105                 110

Leu Pro Lys Ser Leu Phe Glu Gly Leu Phe Ser Leu Gln Leu Leu Leu
        115                 120                 125

Leu Asn Ala Asn Lys Ile Asn Cys Leu Arg Val Asp Ala Phe Gln Asp
    130                 135                 140

Leu His Asn Leu Asn Leu Leu Ser Leu Tyr Asp Asn Lys Leu Gln Thr
145                 150                 155                 160

Val Ala Lys Gly Thr Phe Ser Ala Leu Arg Ala Ile Gln Thr Met His
                165                 170                 175

Leu Ala Gln Asn Pro Phe Ile Cys Asp Cys His Leu Lys Trp Leu Ala
            180                 185                 190

Asp Tyr Leu His Thr Asn Pro Ile Glu Thr Ser Gly Ala Arg Cys Thr
        195                 200                 205

Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Gly Gln Ile Lys Ser Lys
    210                 215                 220

Lys Phe Arg Cys Ser Gly Ser Ala His His His His His His
225                 230                 235


<210>  19
<211>  726
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(726)

<400>  19
atg tac agg atg caa ctc ctg tct tgc att gca cta agt ctt gca ctt       48
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

gtc acg aat tca ctg tcc tcc ggc tcc tgc ccg gcc atg tgc acc tgc       96
Val Thr Asn Ser Leu Ser Ser Gly Ser Cys Pro Ala Met Cys Thr Cys
            20                  25                  30

agc aat ggc atc gtg gac tgt cgt gga aaa ggc ctc act gcc atc ccg      144
Ser Asn Gly Ile Val Asp Cys Arg Gly Lys Gly Leu Thr Ala Ile Pro
        35                  40                  45

gcc aac ctg ccc gag acc atg acg gag ata cgc ctg gag ctg aac ggc      192
```

```
Ala Asn Leu Pro Glu Thr Met Thr Glu Ile Arg Leu Glu Leu Asn Gly
    50                  55                  60

atc aag tcc atc cct cct gga gcc ttc tca ccc tac aga aag cta cgg      240
Ile Lys Ser Ile Pro Pro Gly Ala Phe Ser Pro Tyr Arg Lys Leu Arg
65                  70                  75                  80

agg ata gac ctg agc aac aat cag atc gct gag att gca ccc gac gcc      288
Arg Ile Asp Leu Ser Asn Asn Gln Ile Ala Glu Ile Ala Pro Asp Ala
                85                  90                  95

ttc cag ggc ctc cgc tcc ctg aac tcg ctg gtc ctc tat gga aac aag      336
Phe Gln Gly Leu Arg Ser Leu Asn Ser Leu Val Leu Tyr Gly Asn Lys
            100                 105                 110

atc aca gac ctc ccc cgt ggt gtg ttt gga ggc cta tac acc cta cag      384
Ile Thr Asp Leu Pro Arg Gly Val Phe Gly Gly Leu Tyr Thr Leu Gln
        115                 120                 125

ctc ctg ctc ctg aat gcc aac aag atc aac tgc atc cgg ccc gat gcc      432
Leu Leu Leu Leu Asn Ala Asn Lys Ile Asn Cys Ile Arg Pro Asp Ala
    130                 135                 140

ttc cag gac ctg cag aac ctc tca ctg ctc tcc ctg tat gac aac aag      480
Phe Gln Asp Leu Gln Asn Leu Ser Leu Leu Ser Leu Tyr Asp Asn Lys
145                 150                 155                 160

atc cag agc ctc gcc aag ggc act ttc acc tcc ctg cgg gcc atc cag      528
Ile Gln Ser Leu Ala Lys Gly Thr Phe Thr Ser Leu Arg Ala Ile Gln
                165                 170                 175

act ctg cac ctg gcc cag aac cct ttc att tgc gac tgt aac ctc aag      576
Thr Leu His Leu Ala Gln Asn Pro Phe Ile Cys Asp Cys Asn Leu Lys
            180                 185                 190

tgg ctg gca gac ttc ctg cgc acc aat ccc atc gag acg agt ggt gcc      624
Trp Leu Ala Asp Phe Leu Arg Thr Asn Pro Ile Glu Thr Ser Gly Ala
        195                 200                 205

cgc tgt gcc agt ccc cgg cgc ctc gcc aac aag cgc atc ggg cag atc      672
Arg Cys Ala Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Gly Gln Ile
    210                 215                 220

aag agc aag aag ttc cgg tgc tca ggt agc gct cat cac cat cat cat      720
Lys Ser Lys Lys Phe Arg Cys Ser Gly Ser Ala His His His His His
225                 230                 235                 240

cac tga                                                             726
His
```

<210> 20
<211> 241
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15

Val Thr Asn Ser Leu Ser Ser Gly Ser Cys Pro Ala Met Cys Thr Cys
            20                  25                  30

Ser Asn Gly Ile Val Asp Cys Arg Gly Lys Gly Leu Thr Ala Ile Pro
```

```
        35                  40                  45

Ala Asn Leu Pro Glu Thr Met Thr Glu Ile Arg Leu Glu Leu Asn Gly
    50                  55                  60

Ile Lys Ser Ile Pro Pro Gly Ala Phe Ser Pro Tyr Arg Lys Leu Arg
65                  70                  75                  80

Arg Ile Asp Leu Ser Asn Asn Gln Ile Ala Glu Ile Ala Pro Asp Ala
                85                  90                  95

Phe Gln Gly Leu Arg Ser Leu Asn Ser Leu Val Leu Tyr Gly Asn Lys
            100                 105                 110

Ile Thr Asp Leu Pro Arg Gly Val Phe Gly Gly Leu Tyr Thr Leu Gln
        115                 120                 125

Leu Leu Leu Leu Asn Ala Asn Lys Ile Asn Cys Ile Arg Pro Asp Ala
    130                 135                 140

Phe Gln Asp Leu Gln Asn Leu Ser Leu Leu Ser Leu Tyr Asp Asn Lys
145                 150                 155                 160

Ile Gln Ser Leu Ala Lys Gly Thr Phe Thr Ser Leu Arg Ala Ile Gln
                165                 170                 175

Thr Leu His Leu Ala Gln Asn Pro Phe Ile Cys Asp Cys Asn Leu Lys
            180                 185                 190

Trp Leu Ala Asp Phe Leu Arg Thr Asn Pro Ile Glu Thr Ser Gly Ala
        195                 200                 205

Arg Cys Ala Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Gly Gln Ile
    210                 215                 220

Lys Ser Lys Lys Phe Arg Cys Ser Gly Ser Ala His His His His His
225                 230                 235                 240

His
```

<210> 21
<211> 726
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(726)

<400> 21
atg tac agg atg caa ctc ctg tct tgc att gca cta agt ctt gca ctt 48
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu

```
1               5                   10                  15

gtc acg aat tca gcc aac tcc atc tcc tgc cct tcg ccc tgc acg tgc      96
Val Thr Asn Ser Ala Asn Ser Ile Ser Cys Pro Ser Pro Cys Thr Cys
            20                  25                  30

agc aat aac atc gtg gac tgt cga gga aag ggc ttg atg gag att cct     144
Ser Asn Asn Ile Val Asp Cys Arg Gly Lys Gly Leu Met Glu Ile Pro
        35                  40                  45

gcc aac ttg ccg gag ggc atc gtc gaa ata cgc cta gaa cag aac tcc     192
Ala Asn Leu Pro Glu Gly Ile Val Glu Ile Arg Leu Glu Gln Asn Ser
    50                  55                  60

atc aaa gcc atc cct gca gga gcc ttc acc cag tac aag aaa ctg aag     240
Ile Lys Ala Ile Pro Ala Gly Ala Phe Thr Gln Tyr Lys Lys Leu Lys
65                  70                  75                  80

cga ata gac atc agc aag aat cag ata tcg gat att gct cca gat gcc     288
Arg Ile Asp Ile Ser Lys Asn Gln Ile Ser Asp Ile Ala Pro Asp Ala
                85                  90                  95

ttc cag ggc ctg aaa tca ctc aca tcg ctg gtc ctg tat ggg aac aag     336
Phe Gln Gly Leu Lys Ser Leu Thr Ser Leu Val Leu Tyr Gly Asn Lys
            100                 105                 110

atc acc gag att gcc aag gga ctg ttt gat ggg ctg gtg tcc cta cag     384
Ile Thr Glu Ile Ala Lys Gly Leu Phe Asp Gly Leu Val Ser Leu Gln
        115                 120                 125

ctg ctc ctc ctc aat gcc aac aag atc aac tgc ctg cgg gtg aac acg     432
Leu Leu Leu Leu Asn Ala Asn Lys Ile Asn Cys Leu Arg Val Asn Thr
    130                 135                 140

ttt cag gac ctg cag aac ctc aac ttg ctc tcc ctg tat gac aac aag     480
Phe Gln Asp Leu Gln Asn Leu Asn Leu Leu Ser Leu Tyr Asp Asn Lys
145                 150                 155                 160

ctg cag acc atc agc aag ggg ctc ttc gcc cct ctg cag tcc atc cag     528
Leu Gln Thr Ile Ser Lys Gly Leu Phe Ala Pro Leu Gln Ser Ile Gln
                165                 170                 175

aca ctc cac tta gcc caa aac cca ttt gtg tgc gac tgc cac ttg aag     576
Thr Leu His Leu Ala Gln Asn Pro Phe Val Cys Asp Cys His Leu Lys
            180                 185                 190

tgg ctg gcc gac tac ctc cag gac aac ccc atc gag aca agc ggg gcc     624
Trp Leu Ala Asp Tyr Leu Gln Asp Asn Pro Ile Glu Thr Ser Gly Ala
        195                 200                 205

cgc tgc agc agc ccg cgc cga ctc gcc aac aag cgc atc agc cag atc     672
Arg Cys Ser Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Ser Gln Ile
    210                 215                 220

aag agc aag aag ttc cgg tgc tca ggt agc gct cat cac cat cat cat     720
Lys Ser Lys Lys Phe Arg Cys Ser Gly Ser Ala His His His His His
225                 230                 235                 240

cac tga                                                            726
His
```

<210> 22
<211> 241
<212> PRT
<213> Homo sapiens

<400> 22

Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1 5 10 15

Val Thr Asn Ser Ala Asn Ser Ile Ser Cys Pro Ser Pro Cys Thr Cys
20 25 30

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

Ala Asn Leu Pro Glu Gly Ile Val Glu Ile Arg Leu Glu Gln Asn Ser
50 55 60

Ile Lys Ala Ile Pro Ala Gly Ala Phe Thr Gln Tyr Lys Lys Leu Lys
65 70 75 80

Arg Ile Asp Ile Ser Lys Asn Gln Ile Ser Asp Ile Ala Pro Asp Ala
85 90 95

Phe Gln Gly Leu Lys Ser Leu Thr Ser Leu Val Leu Tyr Gly Asn Lys
100 105 110

Ile Thr Glu Ile Ala Lys Gly Leu Phe Asp Gly Leu Val Ser Leu Gln
115 120 125

Leu Leu Leu Leu Asn Ala Asn Lys Ile Asn Cys Leu Arg Val Asn Thr
130 135 140

Phe Gln Asp Leu Gln Asn Leu Asn Leu Leu Ser Leu Tyr Asp Asn Lys
145 150 155 160

Leu Gln Thr Ile Ser Lys Gly Leu Phe Ala Pro Leu Gln Ser Ile Gln
165 170 175

Thr Leu His Leu Ala Gln Asn Pro Phe Val Cys Asp Cys His Leu Lys
180 185 190

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

Arg Cys Ser Ser Pro Arg Arg Leu Ala Asn Lys Arg Ile Ser Gln Ile
210 215 220

Lys Ser Lys Lys Phe Arg Cys Ser Gly Ser Ala His His His His His
225 230 235 240

His

<210> 23
<211> 1362

<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1362)

<400> 23

```
atg tac agg atg caa ctc ctg tct tgc att gca cta agt ctt gca ctt       48
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                  10                  15

gtc acg aat tca ctt cgt cag gaa gat ttt cca cct cgc att gtt gaa       96
Val Thr Asn Ser Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val Glu
            20                  25                  30

cac cct tca gac ctg att gtc tca aaa gga gaa cct gca act ttg aac      144
His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu Asn
        35                  40                  45

tgc aaa gct gaa ggc cgc ccc aca ccc act att gaa tgg tac aaa ggg      192
Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys Gly
    50                  55                  60

gga gag aga gtg gag aca gac aaa gat gac cct cgc tca cac cga atg      240
Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg Met
65                  70                  75                  80

ttg ctg ccg agt gga tct tta ttt ttc tta cgt ata gta cat gga cgg      288
Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly Arg
                85                  90                  95

aaa agt aga cct gat gaa gga gtc tat gtc tgt gta gca agg aat tac      336
Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn Tyr
            100                 105                 110

ctt gga gag gct gtg agc cac aat gca tcg ctg gaa gta gcc ata ctt      384
Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile Leu
        115                 120                 125

cgg gat gac ttc aga caa aac cct tcg gat gtc atg gtt gca gta gga      432
Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val Gly
    130                 135                 140

gag cct gca gta atg gaa tgc caa cct cca cga ggc cat cct gag ccc      480
Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu Pro
145                 150                 155                 160

acc att tca tgg aag aaa gat ggc tct cca ctg gat gat aaa gat gaa      528
Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp Glu
                165                 170                 175

aga ata act ata cga gga gga aag ctc atg atc act tac acc cgt aaa      576
Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg Lys
            180                 185                 190

agt gac gct ggc aaa tat gtt tgt gtt ggt acc aat atg gtt ggg gaa      624
Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly Glu
        195                 200                 205

cgt gag agt gaa gta gcc gag ctg act gtc tta gag aga cca tca ttt      672
Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser Phe
    210                 215                 220

gtg gag tcc aag tac ggc cct cct tgc cct ccc tgc cct gcc cct gag      720
Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240
```

```
ttc gag ggc gga cct agc gtg ttc ctg ttc cct cct aag cct aag gac      768
Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

acc ctg atg atc tcc cgg acc cct gag gtg acc tgt gtg gtg gtg gac      816
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

gtg tcc cag gag gac cct gag gtc cag ttc aac tgg tac gtg gac ggc      864
Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285

gtg gag gtg cac aac gcc aag acc aag cct cgg gag gag cag ttc aat      912
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
    290                 295                 300

tcc acc tac cgg gtg gtg tct gtg ctg acc gtg ctg cac cag gac tgg      960
Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320

ctg aac ggc aaa gaa tac aag tgt aag gtc tcc aac aag ggc ctg ccc     1008
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
                325                 330                 335

tcc tcc atc gag aaa acc atc tcc aag gcc aag ggc cag cct agg gag     1056
Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

cct cag gtg tac acc ctg cct cct agc cag gaa gag atg acc aag aac     1104
Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
        355                 360                 365

cag gtg tcc ctg acc tgt ctg gtg aag ggc ttc tac cct tcc gac atc     1152
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

gcc gtg gag tgg gag tcc aac ggc cag cct gag aac aac tac aag acc     1200
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

acc cct cct gtg ctg gac tcc gac ggc tcc ttc ttc ctg tac tcc agg     1248
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
                405                 410                 415

ctg acc gtg gac aag tcc cgg tgg cag gag ggc aac gtc ttt tcc tgc     1296
Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
            420                 425                 430

tcc gtg atg cac gag gcc ctg cac aac cac tac acc cag aag tcc ctg     1344
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

tcc ctg tct ctg ggc tga                                            1362
Ser Leu Ser Leu Gly
    450
```

<210> 24
<211> 453
<212> PRT
<213> Homo sapiens

<400> 24

```
Met Tyr Arg Met Gln Leu Leu Ser Cys Ile Ala Leu Ser Leu Ala Leu
1               5                   10                  15
```

```
Val Thr Asn Ser Leu Arg Gln Glu Asp Phe Pro Pro Arg Ile Val Glu
            20                  25                  30

His Pro Ser Asp Leu Ile Val Ser Lys Gly Glu Pro Ala Thr Leu Asn
        35                  40                  45

Cys Lys Ala Glu Gly Arg Pro Thr Pro Thr Ile Glu Trp Tyr Lys Gly
    50                  55                  60

Gly Glu Arg Val Glu Thr Asp Lys Asp Asp Pro Arg Ser His Arg Met
65                  70                  75                  80

Leu Leu Pro Ser Gly Ser Leu Phe Phe Leu Arg Ile Val His Gly Arg
                85                  90                  95

Lys Ser Arg Pro Asp Glu Gly Val Tyr Val Cys Val Ala Arg Asn Tyr
            100                 105                 110

Leu Gly Glu Ala Val Ser His Asn Ala Ser Leu Glu Val Ala Ile Leu
        115                 120                 125

Arg Asp Asp Phe Arg Gln Asn Pro Ser Asp Val Met Val Ala Val Gly
    130                 135                 140

Glu Pro Ala Val Met Glu Cys Gln Pro Pro Arg Gly His Pro Glu Pro
145                 150                 155                 160

Thr Ile Ser Trp Lys Lys Asp Gly Ser Pro Leu Asp Asp Lys Asp Glu
                165                 170                 175

Arg Ile Thr Ile Arg Gly Gly Lys Leu Met Ile Thr Tyr Thr Arg Lys
            180                 185                 190

Ser Asp Ala Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly Glu
        195                 200                 205

Arg Glu Ser Glu Val Ala Glu Leu Thr Val Leu Glu Arg Pro Ser Phe
    210                 215                 220

Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285
```

```
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
    290                 295                 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
                325                 330                 335

Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
        355                 360                 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
                405                 410                 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
            420                 425                 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

Ser Leu Ser Leu Gly
    450
```