

FGF-R4 receptor-specific antagonists

The subject of the present invention is antagonists specific for the FGF receptor 4 (FGF-R4) which make it possible to inhibit the activity of this receptor. These
5 antagonists are in particular antibodies directed specifically against the FGF receptor 4 (FGF-R4).

A subject of the present invention is also the therapeutic use of these antagonists, in particular in the angiogenesis field and in the treatment of certain types of cancer.

10 FGFs (Fibroblast Growth Factors) are among the first molecules described as being capable of stimulating vascular cell proliferation, migration and differentiation *in vitro* and *in vivo*. An abundant literature describes the induction of angiogenesis and the formation of blood capillaries *in vitro* and *in vivo* by FGFs. FGFs are also involved in tumour angiogenesis by promoting the formation of blood vessels recruited by the
15 tumour.

The human FGF family is composed of at least 23 members which all have a conserved central domain of 120 amino acids. They exert their biological activity by interacting with their high affinity receptors of tyrosine-kinase type (FGF-R) and
20 heparan sulphate proteoglycans, which are components present on most cell surfaces and extracellular matrices (low-affinity binding site), so as to form a ternary complex. Some FGFs have a high affinity for several FGF-Rs, whereas others activate specifically one receptor or one isoform of a receptor.

25 An FGF-R4-specific ligand has been identified by Xie and al (Cytokine, 1999, 11:729-35.) This ligand, called FGF19, is a ligand with high affinity for FGF-R4 exclusively, and the binding of which to the receptor is heparin-dependent or heparan sulphate-dependent. FGF19 has been identified in adult animals, only in the hepatocytes and the small intestine where it regulates the synthesis of bile acid by
30 the liver. It appears to be a growth factor involved during embryonic development, and appears to be involved in foetal brain development in the zebra fish and humans.

Other FGF-R4 ligands are described, such as FGF1 or FGF2. These ligands strongly

activate FGF-R4, but are not specific of FGF-R4: they also bind to other FGF-Rs (Ornitz and al., *J. Biol. Chem.*, 1996, 271:15292-7).

- The activation of the FGF-R4 receptor results in several types of cell signalling.
- 5 Among these, the most conventional form corresponds to the setting up of a phosphorylation cascade-mediated signalling pathway subsequent to stimulation of FGF-R4 by FGF. This induction results in the autophosphorylation of the tyrosine kinase domain of FGF-R4 and serves to initiate an intracellular signalling pathway dependent on the phosphorylation of other signalling proteins such as AKT, p44/42,
- 10 JNK etc. This phosphorylation-mediated signalling varies according to the cell type and according to the coreceptors or the adhesion molecules present at the surface of these cells (Cavallaro and al., *Nat. Cell Biol.* 3/7, 650-657 (2001); Stadler and al., *Cell. Signal.* 18/6, 783-794. (2006); Lin and al., *J Biol Chem.*, 2007, 14:27277-84. (2007)). Another method of signalling that is important for FGF-Rs, including FGF-
- 15 R4, is the internalization of the receptor after activation in combination with its ligand. This mechanism is not dependent on the tyrosine kinase activity of the receptor, but on a short C-terminal sequence of FGF-R4 (Klingenberg and al., *J. Cell Sci.*, 113/Pt10:1827-1838 (2000)).
- 20 Four distinct forms of FGF-R4 are described in the literature. A full-length form with 2 polymorphic variants at position 388, namely FGF-R4 Gly388, which is the normal form of the receptor, and the Arg388 form which is described in the context of several tumours (Bange and al., *Cancer Res.* 62/3, 840-847 (2002); Spinola and al., *J Clin Oncol* 23, 7307-7311(2005); Stadler and al., *Cell. Signal.* 18/6, 783-794. (2006)). A soluble form, which is expressed in mammary tumour cells, has also been
- 25 discovered (Takaishi and al., *Biochem Biophys Res Commun.*, 2000, 267:658-62). A fourth form, which is truncated in the extracellular portion, has been described in certain hypophyseal adenomas (Ezzat and al., *J Clin Invest.*, 2002, 109:69-78).
- FGF-R4 is mainly expressed in tissues derived from the endoderm, such as the
- 30 gastrointestinal tract, the pancreas, the liver, the muscles and the adrenal glands.

FGF-R4 is known in the literature as having several cellular roles, the principal three of which are described below:

Firstly, this receptor is involved in the control of various cell differentiation processes *in vitro* and *in vivo*, such as skeletal muscle differentiation and regeneration, mesenchymal tissue differentiation, or osteogenesis, or else in the formation of alveoli during post-natal hepatic development.

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Secondly, FGF-R4 is described in the control of bile acid and cholesterol homeostasis and is thought to be involved in the control of adiposity. Furthermore, the balance between bile acid production and cholesterol production is controlled by FGF-R4 *in vitro* and *in vivo*.

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Thirdly, FGF-R4 is involved in certain tumoral phenomena such as the development of hepatocellular carcinomas or colon cancers, or in the proliferation of mammary fibroadenoma cells or of mammary cancer epithelial cells, such as mammary or colorectal carcinoma cell motility. The tumoral involvement of FGF-R4 is predominantly associated with the appearance of the polymorphism (Gly388Arg) correlated with the acceleration of tumour progression in mammary and colorectal tumours (Bange and al., *Cancer Res.* 62/3, 840-847, 2002), prostate tumours (Wang and al., *Clin. Cancer Res.* 10/18, 6169-6178, 2004) or hepatic tumours (Nicholes and al., *Am. J. Pathol.* 160/6, 2295-307, 2002). This polymorphism is also associated with a poor prognosis in the case of sarcomas (Morimoto and al., *Cancer* 98/10, 2245-2250, 2003), of pulmonary adenocarcinomas (Spinola and al., *J Clin Oncol* 23, 7307-7311, 2005) or of squamous sarcomas (da Costa Andrade and al., *Exp Mol Pathol* 82, 53-7, 2007). The overexpression of FGF-R4 is also described in certain pancreatic cancer lines (Shah and al., *Oncogene* 21/54, 8251-61, 2002) and correlates with astrocytoma malignancy (Yamada and al., *Neurol. Res.* 24/3, 244-8, 2002). In addition, the use of an anti-FGF19 monoclonal antibody in *in vivo* models of colon tumour xenografts or in hepatocellular carcinoma models shows that the inactivation of FGF19 and therefore the blocking of FGF-R4 activation can be beneficial in the treatment of colon or liver cancer.

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It is accepted in the literature that the FGF/FGF-R1 and FGF/FGF-R2 pairs participate in the formation of new blood vessels in a normal or pathological context. However, the potential involvement of FGF-R4 in the control of this cell phenomenon has never been studied. It has, in fact, up until now been supposed that the

activation of angiogenesis is mediated by FGF-R1 and/or FGF-R2 (Presta and al, Cytokine Growth Factor Rev., 2005, 16:159-78).

Examples of FGF-R4 antagonists are described in the literature, in particular: small
5 molecules, but they do not target FGF-R4 specifically, thus leading to adverse effects. Thus, tyrosine-kinase domain-inhibiting small chemical molecules which inhibit several FGF-Rs and also other receptor tyrosine kinases have been described by Thompson and al. (Thompson and al *J Med Chem.*, 2000, 43:4200-11.). Small
10 chemical molecules which inhibit FGF-Rs by association with their extracellular portion have also been described in application WO2007/080325.

Antibodies have also been studied, such as the anti-FGFR1 and/or anti-FGFR4 antibodies described in international applications WO2005/066211 and WO2008052796 or by Chen and al. (*Hybridoma* 24/3, 152-159, 2005). Application
15 WO2005/037235 describes antibodies which are FGF-R antagonists, for the treatment of obesity and diabetes. In addition, anti-FGF-R4 antibodies which are agonists are described in application WO03/063893.

The subject of the present invention is an FGF-R4 receptor antagonist, characterized in that it binds specifically to said FGF-R4 receptor.

20 Advantageously, said antagonist is an antibody specific for the FGF-R4 receptor.

In one embodiment, the antagonist which is the subject of the invention binds to the D2-D3 domain of the FGF-R4 receptor. In one advantageous embodiment, the antagonist which is the subject of the invention binds to the D2 domain of the FGF-
25 R4 receptor. In an even more advantageous embodiment, the antagonist binds to the sequence SEQ ID No. 70.

Advantageously, the FGF-R4 receptor-specific antagonist has a K_D with respect to the FGF-R4 receptor, determined by the Biacore technique, of less than 10^{-8} M, less
30 than 5×10^{-9} M, less than 2×10^{-9} M or less than 1×10^{-9} M.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist is active against both human FGF-R4 and murine FGF-R4.

In another advantageous embodiment, the FGF-R4 receptor-specific antagonist is

active at the same time against human FGF-R4, murine FGF-R4 and rat FGF-R4.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody comprises at least one CDR having a sequence identical to SEQ ID No. 9, 10, 11,
5 12, 13, 14, 73, 74, 75, 78, 79, 80, 83, 84, 85, 88, 89, 90, 93, 94, 95, 98, 99, 100, 103, 104, 105, 108, 109 or 110 or at least one CDR of which the sequence differs by one or two amino acids compared with the sequences SEQ ID No. 9, 10, 11, 12, 13, 14, 73, 74, 75, 78, 79, 80, 83, 84, 85, 88, 89, 90, 93, 94, 95, 98, 99, 100, 103, 104, 105, 108, 109 or 110, provided that the antibody keeps its binding specificity.

10 In one particularly advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody comprises the CDRs of sequence SEQ ID No. 9, 10, 11, 12, 13, 14, 73, 74, 75, 78, 79, 80, 83, 84, 85, 88, 89, 90, 93, 94, 95, 98, 99, 100, 103, 104, 105, 108, 109 or 110 or CDRs of which the sequences differ by one or two amino acids compared, respectively, with the abovementioned sequences, provided that
15 this does not modify the FGF-R4 receptor-binding specificity of the antibody.

In one advantageous embodiment, the antibodies of the invention comprise at least one heavy chain and at least one light chain, said heavy chain comprising three CDR sequences having amino acid sequences selected from the group constituted of SEQ ID No. 9, 10 and 11 or 73, 74 and 75, 83, 84 and 85, or 93, 94 and 95, or 103,
20 104 and 105, said light chain comprising three CDR sequences having amino acid sequences selected from the group constituted of SEQ ID No. 12, 13 and 14 or 78, 79 and 80, or 88, 89 and 90, or 98, 99 and 100, or 108, 109 and 110.

In one advantageous embodiment, the heavy chain variable regions of the FGF-R4
25 receptor-specific antagonist antibody comprise a sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 6, 77, 87, 97 or 107.

In one advantageous embodiment, the light chain variable regions of the FGF-R4 receptor-specific antagonist antibody comprise a sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 8, 72, 82, 92 or 102.

30 A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising a heavy chain comprising a variable region encoded by a nucleotide sequence having at least 80%, 90%, 95% or 99% identity with sequence SEQ ID No. 5, 76, 86, 96 or 106.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist

antibody comprising a light chain comprising a variable region encoded by a nucleotide sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 7, 71, 81, 91 or 101.

5 A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising a heavy chain comprising a variable region of polypeptide sequence SEQ ID No. 6, 77, 87, 97 or 107.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising a light chain comprising a variable region of polypeptide sequence SEQ ID No. 8, 72, 82, 92 or 102.

10 A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising sequences encoded by the nucleotide sequences SEQ ID Nos. 5 and 7 or 71 and 76, or 81 and 86, or 91 and 96, or 101 and 106.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising the polypeptide sequences SEQ ID Nos. 6 and 8, or 72 and 77,
15 or 82 and 87, or 92 and 97 or 102 and 107.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody comprises sequences at least 80%, 90%, 95% or 99% identical to SEQ ID No. 2 and/or SEQ ID No. 4; or SEQ ID No. 72 and/or SEQ ID No. 77; or SEQ ID No. 82 and/or SEQ ID No. 87; or SEQ ID No. 92 and/or SEQ ID No. 97; or SEQ ID No. 102
20 and/or SEQ ID No. 107.

In one particularly advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody comprises a heavy chain encoded by a nucleotide sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 1.

25 A subject of the present invention is also an FGF-R4 receptor antagonist antibody comprising a heavy chain of polypeptide sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 2.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising a light chain encoded by a nucleotide sequence at least 80%,
30 90%, 95% or 99% identical to the sequence SEQ ID No. 3.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody comprising a light chain of polypeptide sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 4.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist

antibody comprising the sequences encoded by the nucleotide sequences SEQ ID No. 1 and 3.

In one even more advantageous embodiment, the FGF-R4-specific antagonist antibody comprises a heavy chain comprising the sequence SEQ ID No. 2 and a
5 light chain comprising the sequence SEQ ID No. 4.

The antibody composed of a heavy chain of sequence SEQ ID No. 2 and of a light sequence SEQ ID No. 4 will be called 40-12 in the rest of the application.

10 In one embodiment of the invention, the FGF-R4-specific antibodies are active at the same time against human FGF-R4, murine FGF-R4 and rat FGF-R4.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist induces inhibition of AKT/p38 cell pathways.

15 In one advantageous embodiment, the FGF-R4 receptor-specific antagonist induces inhibition of Erk1/2 cell pathways.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist induces inhibition of FGF-R4-controlled cell signalling pathways.

20 In another advantageous embodiment, the FGF-R4 receptor-specific antagonist induces inhibition of tumour cell proliferation.

In yet another advantageous embodiment, the FGF-R4 receptor-specific antagonist induces inhibition of angiogenesis.

25 In another particularly advantageous embodiment, the FGF-R4 receptor-specific antagonist has an affinity for FGF-R4 which is 10 times greater than its affinity for the other FGF receptors.

In one particularly advantageous embodiment, the antibody according to the
30 invention is an FGF-R4 receptor-specific humanized antagonist antibody.

In one embodiment, the FGF-R4 receptor-specific humanized antagonist antibody comprises a light chain of which the variable region is encoded by a nucleotide sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 29 or the sequence SEQ ID No. 31.

In another embodiment, the FGF-R4 receptor-specific humanized antagonist antibody comprises a light chain of which the variable region is at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 30 or to the sequence SEQ ID No. 32.

- 5 In another embodiment, the FGF-R4 receptor-specific humanized antagonist antibody comprises a light chain in which the variable region is encoded by a sequence identical to the nucleotide sequence SEQ ID No. 29 or to the sequence SEQ ID No. 31.

- 10 A subject of the present invention is also an FGF-R4 receptor-specific humanized antagonist antibody comprising a heavy chain of which the variable region is encoded by a sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 33, to the sequence SEQ ID No. 35 or to the sequence SEQ ID No. 37.

- A subject of the present invention is also an FGF-R4 receptor-specific humanized antagonist antibody comprising a heavy chain of which the variable region is at least
15 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 34, to the sequence SEQ ID No. 36 or to the sequence SEQ ID No. 38.

A subject of the present invention is also an FGF-R4 receptor-specific humanized antagonist antibody comprising a heavy chain encoded by a nucleotide sequence SEQ ID No. 33 and/or SEQ ID No. 35 and/or SEQ ID No. 37.

- 20 A subject of the present invention is also an FGF-R4 receptor-specific humanized antagonist antibody of which the humanized sequences of sequence SEQ ID No. 30 or 32 are used in combination with the humanized sequences of sequence SEQ ID No. 34, 36 or 38.

- In another embodiment, the FGF-R4 receptor-specific antagonist antibody comprises
25 the CDRs of sequence SEQ ID Nos. 73, 74, 75, 78, 79 and 80 or CDRs of which the sequences differ by one or two amino acids compared, respectively, with the abovementioned sequences, provided that this does not modify the FGF-R4 receptor-binding specificity of the antibody.

- In another embodiment, the FGF-R4 receptor-specific antagonist antibody comprises
30 the CDRs of sequence SEQ ID Nos. 83, 84, 85, 88, 89 and 90 or CDRs of which the sequences differ by one or two amino acids compared, respectively, with the abovementioned sequences, provided that this does not modify the FGF-R4 receptor-binding specificity of the antibody.

In another embodiment, the FGF-R4 receptor-specific antagonist antibody comprises

the CDRs of sequence SEQ ID Nos. 93, 94, 95, 98, 99 and 100 or CDRs of which the sequences differ by one or two amino acids compared, respectively, with the abovementioned sequences, provided that this does not modify the FGF-R4 receptor-binding specificity of the antibody.

5 In another embodiment, the FGF-R4 receptor-specific antagonist antibody comprises the CDRs of sequence SEQ ID Nos. 103, 104, 105, 108, 109 and 110 or CDRs of which the sequences differ by one or two amino acids compared, respectively, with the abovementioned sequences, provided that this does not modify the FGF-R4 receptor-binding specificity of the antibody.

10 In one preferred embodiment of the invention, the FGF-R4 receptor-specific antagonist antibody comprises the CDRs of sequence SEQ ID Nos. 83, 84, 85, 88, 89 and 90.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody
15 is a human antibody of which the heavy chain variable regions comprise a nucleotide sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 76, 86, 96 or 106.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody is a human antibody of which the light chain variable regions comprise a nucleotide
20 sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 71, 81, 91 or 101.

A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising a heavy chain comprising a variable region encoded by a protein sequence having at least 80%, 90%, 95% or 99% identity with the
25 sequence SEQ ID No. 77, 87, 97 or 107.

A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising a light chain comprising a variable region encoded by a protein sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 72, 82, 92 or 102.

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A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising sequences encoded by the nucleotide sequences SEQ ID Nos. 71 and 76 or the nucleotide sequences SEQ ID Nos. 81 and 86 or the nucleotide sequences SEQ ID Nos. 91 and 96 or the nucleotide sequences SEQ ID

Nos. 101 and 106.

A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising the polypeptide sequences SEQ ID Nos. 72 and 77 or the polypeptide sequences SEQ ID Nos. 82 and 87 or the polypeptide sequences
5 SEQ ID Nos. 92 and 97 or the polypeptide sequences SEQ ID Nos 102 and 107.

In one advantageous embodiment, the FGF-R4 receptor-specific antagonist antibody comprises sequences at least 80%, 90%, 95% or 99% identical to SEQ ID No. 72 and/or SEQ ID No. 77.

10 In another advantageous embodiment, the FGF-R4 receptor-specific human antagonist antibody comprises sequences at least 80%, 90%, 95% or 99% identical to SEQ ID No. 82 and/or SEQ ID No. 87.

In another advantageous embodiment, the FGF-R4 receptor-specific human antagonist antibody comprises sequences at least 80%, 90%, 95% or 99% identical
15 to SEQ ID No. 92 and/or SEQ ID No. 97.

In another advantageous embodiment, the FGF-R4 receptor-specific human antagonist antibody comprises sequences at least 80%, 90%, 95% or 99% identical to SEQ ID No. 102 and/or SEQ ID No. 107.

20 In one preferred embodiment, a subject of the present invention is an FGF-R4 receptor-specific human antagonist antibody comprising a light chain encoded by a nucleotide sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 82 and comprising a light chain of polypeptide sequence at least 80%, 90%, 95% or 99% identical to the sequence SEQ ID No. 87.

25 Even more preferably, a subject of the present invention is an FGF-R4 receptor-specific human antagonist antibody comprising sequences encoded by the nucleotide sequences SEQ ID Nos. 82 and 87.

The antibody composed of a heavy chain of sequence SEQ ID No. 77 and of a light
30 sequence SEQ ID No. 72 will be called clone 8 in the rest of the application.

The antibody composed of a heavy chain of sequence SEQ ID No. 87 and of a light sequence SEQ ID No. 82 will be called clone 31 in the rest of the application.

The antibody composed of a heavy chain of sequence SEQ ID No. 97 and of a light sequence SEQ ID No. 92 will be called clone 33 in the rest of the application.

The antibody composed of a heavy chain of sequence SEQ ID No. 107 and of a light sequence SEQ ID No. 102 will be called clone 36 in the rest of the application.

5 The field of the present invention is not limited to the antibodies comprising these sequences. In fact, all the antibodies that specifically bind to FGF-R4, having an antagonistic action on this receptor, are part of the field of the present invention.

A subject of the present invention is also an FGF-R4 receptor-specific antagonist antibody conjugated to a cytotoxic agent.

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A subject of the present invention is the use of an FGF-R4 receptor-specific antagonist in the treatment of diseases associated with angiogenesis.

A subject of the present invention is the use of an FGF-R4 receptor-specific antagonist in the treatment of a cancer.

15 A subject of the present invention is the use of an FGF-R4 receptor-specific antagonist in the treatment of hepatocarcinomas or of any other type of hepatic cancer.

A subject of the present invention is the use of an FGF-R4 receptor-specific antagonist in the treatment of pancreatic cancer.

20 A subject of the present invention is an FGF-R4 receptor-specific antibody which is of use both in the treatment of diseases associated with angiogenesis and in the treatment of hepatocarcinomas or of any other type of hepatic cancer.

A subject of the present invention is an FGF-R4 receptor-specific antibody which is of use at the same time in the treatment of diseases associated with angiogenesis, in
25 the treatment of hepatocarcinomas or of any other type of hepatic cancer, and in the treatment of pancreatic cancer, or cancer of the organs of the gastrointestinal tract or any other organ expressing FGF-R4.

A subject of the present invention is a pharmaceutical composition comprising an
30 FGF-R4 receptor-specific antagonist and excipients.

A subject of the present invention is a method of treating a cancer, comprising the administration, to the patient, of an FGF-R4 receptor-specific antagonist antibody.

A subject of the present invention is a method of treating a disease associated with a

pathological increase in angiogenesis, comprising the administration, to the patient, of an FGF-R4 receptor-specific antagonist antibody.

A subject of the present invention is a method of selecting an FGF-R4 receptor-specific antagonist monoclonal antibody, comprising the following steps:

- 5 a. immunizing mice,
- b. taking lymph nodes from the mice, and
- c. screening the hybridoma supernatants.

10 A subject of the present invention is a cell line that produces FGF-R4 receptor-specific antagonist antibodies.

A subject of the present invention is a method of producing an FGF-R4 receptor-specific antagonist antibody, comprising culturing a cell line that produces FGF-R4
15 receptor antagonist antibodies.

A subject of the present invention is a drug comprising an FGF-R4 receptor-specific antagonist.

20 A subject of the present invention is also a polynucleotide encoding a polypeptide selected from the group constituted of SEQ ID Nos. 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 30, 32, 34, 36, 38, 72, 73, 74, 75, 77, 78, 79, 80, 82, 83, 84, 85, 87, 88, 89, 90, 92, 93, 94, 95, 97, 98, 99, 100, 102, 103, 104, 105, 107, 108, 109 and 110, and the sequences at least 80%, 90%, 95% or 99% identical to one of these sequences.

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A subject of the present invention is a recombinant vector comprising a polynucleotide as described above or encoding a polypeptide as described above.

In order to enable the expression of heavy chains and/or light chains of the FGF-R4
30 receptor antagonist antibody, which is a subject of the invention, the polynucleotides encoding said chains are inserted into expression vectors. These expression vectors may be plasmids, YACs, cosmids, retroviruses, EBV-derived episomes, and any of the vectors that those skilled in the art may deem appropriate for the expression of said chains.

A subject of the present invention is a host cell comprising a recombinant vector as described above.

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Detailed description of the invention

10 A subject of the present invention is the use of antibodies specifically directed against FGF-R4 (without cross-reaction with FGF-R1, R2 or R3) for inhibiting angiogenesis and tumour growth.

Unexpectedly, the inventors have shown that FGF-R4 plays an active and specific role in the control of angiogenesis.

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This function of FGF-R4 had never previously been shown or proposed. Consequently, this receptor may be used as a target for treating pathologies exhibiting an angiogenic dysfunction. The FGF-R4 ligands capable of modulating the activity of said receptor are therefore potential therapeutic agents for numerous
20 angiogenesis-related pathologies.

The present invention can therefore be used in the treatment of all pathologies involving a dysregulation of angiogenesis and requiring inhibition thereof. The pathologies covered may be cancer, with the use of the antagonists according to the
25 invention as tumour angiogenesis inhibitors, or pathologies for which a dysregulation of angiogenesis is described, such as: age-related macular degeneration or ARMD, inflammatory diseases such as rheumatoid arthritis, osteoarthritis, colitis, ulcers or any inflammatory disease of the intestines, atherosclerosis, or else in the treatment of obesity.

30 The use of these antibodies is also illustrated in the inhibition of tumour growth. The antagonists according to the present invention can therefore be used for the treatment of certain cancers involving a dysregulation of FGF-R4, and more particularly, liver cancer, colon cancer, breast cancer, lung cancer, prostate cancer, pancreatic cancer, skin cancer or oesophageal cancer.

One of the major advantages of the antagonists according to the present invention is to specifically target an FGF receptor, in the case in point FGF-R4. This specificity makes it possible to limit the adverse effects that small chemical molecules which inhibit the tyrosine kinase domain can have. In addition, since FGF-R4 is not expressed ubiquitously, but is in particular expressed on endothelial cells, for instance on hepatocyte cells, biliary cells, mammary cells, prostatic cells, ovarian cells, pancreatic cells or renal cells, this provides a method of treating diseases related to a dysregulation of FGF-R4 activity which limits the side effects.

The term "antagonist" refers to any ligand capable of reducing or completely inhibiting the activity of FGF-R4. This antagonist compound is thus also referred to as FGF-R4 inhibitor.

This antagonist may be any FGF-R4 ligand, such as a chemical molecule, a recombinant protein, an oligosaccharide, a polysaccharide, an oligonucleotide or an antibody capable of specifically binding to the FGF-R4 receptor, with the exclusion of any other FGFR.

A subject of the invention is therefore an FGF-R4-specific antagonist. According to the invention, an antagonist that binds specifically to FGF-R4 refers to a ligand which does not bind to the other FGF receptors, namely FGF-R1, FGF-R2 or FGF-R3. In particular, an FGF-R4-specific antibody is an antibody which does not exhibit any cross-reaction with FGF-R1, FGF-R2 or FGF-R3.

"Specific binding" refers to a difference, by a factor of at least 10, between the intensity of the binding to one receptor compared with another, in this case between the binding to FGF-R4 and the possible bindings to FGF-R1, FGF-R2 or FGF-R3.

In one embodiment of the invention, the FGF-R4 ligand is an oligosaccharide or a polysaccharide.

An "oligosaccharide" refers to any saccharide polymer containing from three to ten units of simple sugars. Natural oligosaccharides such as, for example, fructo-oligosaccharides (FOS), and synthetic oligosaccharides such as, for example, heparin-mimetic antithrombotics, exist.

The term "polysaccharide" refers to any polymer constituted of more than ten monosaccharides linked to one another by glycosidic linkages. Natural polysaccharides such as, for example, mucopolysaccharides, fucoids, carrageenans or bacterial exopolysaccharides exist, as do synthetic polysaccharides. Thus, low-
5 molecular-weight fucoidans or highly sulphated exopolysaccharides have shown pro-angiogenic activities (Chabut and al., *Mol Pharmacol.*, 2003, 64:696-702; Matou and al., *Biochem Pharmacol.*, 2005, 69:751-9). Conversely, heparin-derived weakly sulphated oligosaccharides or phosphomannopentose sulphates can have anti-angiogenic characteristics (Parish and al., 1999, 15:3433-41; Casu and al., *J Med*
10 *Chem.*, 2004, 12:838-48)

In one embodiment of the invention, the FGF-R4 ligand is an antibody.

The term "antibody" refers to antibodies or derived molecules of any type, such as
15 polyclonal and monoclonal antibodies. Included among the molecules derived from monoclonal antibodies are humanized antibodies, human antibodies, multispecific antibodies, chimeric antibodies, antibody fragments, nanobodies, etc.

In one embodiment of the invention, the FGF-R4-specific antagonist is a polyclonal
20 antibody.

A "polyclonal antibody" is an antibody which has been produced from a mixture of antibodies originating from several B lymphocyte clones and which recognize a series of different epitopes.

25 In one advantageous embodiment, the FGF-R4-specific antagonist is a monoclonal antibody.

A "monoclonal antibody" is an antibody obtained from a substantially homogeneous population of antibodies derived from a single type of B lymphocyte, clonally amplified. The antibodies making up this population are identical except for possible
30 naturally occurring mutations that may be present in minor amounts. These antibodies are directed against a single epitope and are therefore highly specific.

The term "epitope" refers to the site of the antigen to which the antibody binds. If the antigen is a polymer, such as a protein or a polysaccharide, the epitope may be

made up of contiguous or noncontiguous residues.

In one advantageous embodiment of the invention, the anti-FGF-R4 antagonist antibody binds to an epitope belonging to the D2-D3 domain of the FGF-R4 receptor.

5 In an even more advantageous embodiment, the antibody binds to an epitope included in the domain comprising amino acids 144 to 365 of the FGF-R4 receptor.

In an even more advantageous embodiment, the antibody binds to an epitope included in the D2 domain of the FGF-R4 receptor, this epitope corresponding to amino acids 145 to 242 described in the sequence SEQ ID No. 70.

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An antibody, also known as an immunoglobulin, is composed of two identical heavy chains ("VH") and of two identical light chains ("VL") which are linked by a disulphide bridge. Each chain contains a constant region and a variable region. Each variable region comprises three segments called "complementarity determining regions" (15 "CDRs") or "hypervariable regions", which are mainly responsible for the binding to the epitope of an antigen.

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The term "VH" refers to the variable regions of an immunoglobulin heavy chain of an antibody, including the heavy chains of an Fv, scFv, dsFv, Fab, Fab' or F(ab)' fragment.

The term "VL" refers to the variable regions of an immunoglobulin light chain of an antibody, including the light chains of an Fv, scFv, dsFv, Fab, Fab' or F(ab)' fragment.

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The term "antibody fragment" refers to any part of said antibody: Fab (fragment antigen binding), Fv, scFv (single chain Fv), Fc (fragment crystallizable). Preferably, these functional fragments will be fragments of the type Fv, scFv, Fab, F(ab')₂, Fab', scFv-Fc or diabodies, which generally have the same binding specificity as the (30 chimeric or humanized, monoclonal antibody from which they are derived. According to the present invention, antibody fragments of the invention can be obtained from chimeric or humanized, monoclonal antibodies by methods such as digestion with enzymes, for instance pepsin or papain, and/or by cleavage of the disulphide bridges by chemical reduction.

The term "CDR regions or CDRs" is intended to denote the immunoglobulin heavy and light chain hypervariable regions as defined by Kabat and al. (Kabat and al., Sequences of proteins of immunological interest, 5th Ed., U.S. Department of Health and Human Services, NIH, 1991, and later editions). There are 3 heavy chain CDRs and 3 light chain CDRs. The term CDR or CDRs is used herein to denote, as appropriate, one or more of these regions or even all of these regions which contain the majority of the amino acid residues responsible for the affinity binding of the antibody for the antigen or the epitope that it recognizes. The most conserved regions of the variable domain are called FR (for "framework") regions or sequences.

In another embodiment of the invention, the FGF-R4-specific antagonist is a chimeric antibody.

The term "chimeric antibody" refers to an antibody in which the constant region, or a portion thereof, is altered, replaced or exchanged, such that the variable region is linked to a constant region of a different species, or belongs to another antibody class or subclass.

The term "chimeric antibody" also refers to an antibody in which the variable region, or a portion thereof, is altered, replaced or exchanged, such that the constant region is linked to a variable region of a different species, or belongs to another antibody class or subclass.

The methods of producing chimeric antibodies are known to those skilled in the art. See, for example, Morrison, 1985, *Science*, **229**:1202; Oi and al., 1986, *Bio Techniques*, **4**:214; Gillies and al., 1989, *J. Immunol. Methods*, **125**:191-202; U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397.

These chimeric versions of the antibody may comprise the fusion of the VL and VH variable regions to the Ckappa and the CH (IgG1) constant domains of human origin in order to generate a chimeric monoclonal antibody.

The CH (IgG1) domain can also be modified by point mutations in order to increase the affinity of the Fc fragment for the FcγR1IIa receptor and thereby to increase the effector functions of the antibody (Lazar and al., 2006, *Proc. Natl. Acad. Sci. USA* **103**: 4005-4010; Stavenhagen and al., 2007, *Cancer Res.* **67**: 8882-8890).

The present invention includes the humanized versions of the antibodies.

The term "humanized antibody" refers to an antibody which contains mainly human immunoglobulin sequences. This term generally refers to a non-human
5 immunoglobulin which has been modified by incorporation of human sequences or of residues found in human sequences.

In general, humanized antibodies comprise one or typically two variable domains in which all or part of the CDR regions correspond to parts derived from the non-human
10 parent sequence and in which all or part of the FR regions are those derived from a human immunoglobulin sequence. The humanized antibody can then comprise at least one portion of an immunoglobulin constant region (Fc), in particular that of the human immunoglobulin template chosen.

The goal is thus to have an antibody that is minimally immunogenic in a human.
15 Thus it is possible that one or two amino acids in one or more CDRs can be modified by one that is less immunogenic to a human host, without substantially reducing the specific binding function of the antibody to FGF-R4. Similarly, the residues of the framework regions may not be human, and it is possible for them not to be modified since they do not contribute to the immunogenic potential of the antibody.

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Several methods of humanization known to those skilled in the art exist for modifying a non-human parent antibody so as to give an antibody that is less immunogenic to humans. An overall sequence identity with a human antibody is not necessarily required. This is because the overall sequence identity is not necessarily a predictive
25 indicator of reduced immunogenicity, and the modification of a limited number of residues can result in humanized antibodies having a greatly reduced immunogenic potential in humans (Molecular Immunology (2007) 44, 1986-1998).

Various methods are, for example, CDR grafting (EPO 0 239 400; WO 91/09967; and U.S. Pat. Nos. 5,530,101 and 5,585,089), resurfacing (EPO 0 592 106; EPO 0 519 596; Padlan, 1991, Molec Imm 28(4/5):489-498; Studnicka and al., 1994, Prot Eng 7(6):805-814; and Roguska and al., 1994, PNAS 91:969-973) or else chain
30 shuffling (U.S. Pat. No. 5,565,332).

The present invention relates in particular to humanized antibodies of which the variable portions are modified according to the following technology:

The light and heavy chains most similar to the corresponding chains of the anti-FGF-R4 murine antibody 40-12 are identified by comparison with the Protein Data Bank (H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne. *Nucleic Acids Research*, 2000, 28:235-242). The sequence alignment uses the BLAST algorithm (*J Mol Biol.* 1990 Oct 215:403-410). These are tridimensional structures corresponding to the PDB codes 1NDM & 1ETZ respectively used to build up the homology models of the variable domain light and heavy chains. These tridimensional models are subsequently energy minimized using the standard procedure implemented in the MOE software (Molecular Operating Environment, Chemical Computing Group, Quebec, Canada). A molecular dynamic (MD) simulation of these minimized tridimensional models of the antibody is subsequently performed with the Amber software (D.A. Case, T.E. Cheatham, III, T. Darden, H. Gohlke, R. Luo, K.M. Merz, Jr., A. Onufriev, C. Simmerling, B. Wang and R. Woods. *J. Computat. Chem.* 2005, 26:1668-1688). This simulation is done with harmonic constraints applied to the protein backbone atoms at a temperature of 500 K for a period of 1.1 nanoseconds in a generalized Born implicit solvent (Gallicchio & Levy, *J Comput Chem* 2004, 25:479-499). Ten diverse conformations are thus extracted from this first simulation, one tridimensional conformation every one hundred picoseconds, during the last nanosecond of the simulation. These ten diverse conformations are then each subjected to a molecular dynamic simulation, without constraints on the protein backbone, at a temperature of 27°C for 2.3 nanoseconds in a generalized Born implicit solvent. The bonds involving a hydrogen atom are constrained using the SHAKE algorithm (Barth. and al., *J Comp Chem*, 1995, 16:1192-1209), the time step is 1 femtosecond, and the simulation was run based on the Langevin equation at constant volume and a constant temperature of 27°C. For each of the ten molecular dynamic simulations, the last two thousand conformations, extracted at a frequency of one every picosecond, are then used to quantify, for each amino acid of the antibody to be humanized, the deviation of the atomic positions with respect to an average, or medoid, conformation of the amino acid. The Scientific Vector Language (SVL) of the MOE software is used to code all of the analysis described below. The medoid conformation of the amino acid is the conformation derived from the molecular dynamic which is the closest to the average

conformation calculated from the position of the atoms of all the conformations of the amino acid. The distance used for detecting the medoid conformation is the route mean square (RMSD) of the scalar distances between the atoms of two conformations of the amino acid. Similarly, the deviation of the positions of the atoms of one conformation of an amino acid compared with the medoid conformation is quantified by calculating the RMSD of the scalar distances between the atoms of the amino acid of one conformation of the simulation and the same atoms of the medoid conformation. Subsequently, by comparing the RMSD of the positions of the atoms of a given amino acid (i), averaged over all the ten molecular dynamic simulations (Fi), with the RMSD of the positions of all the amino acids of the antibody, averaged over all the ten molecular dynamic simulations (Fm), it is decided whether the amino acid is flexible enough to be considered able to potentially interact with the T-cell receptors and trigger activation of the immune system. An amino acid i is considered flexible if its flexibility score Zi, defined as $Z_i = (F_i - F_m)/F_m$, is above 0.15. 45 amino acids are thus identified as flexible in the variable domain of the antibody, with the exclusion of the antigen complementarity determining region (CDR) and of its immediate vicinity. The immediate vicinity of the CDR is defined as any amino acid with an alpha carbon at a distance of 5 angströms (Å) or less to an alpha carbon of the CDR.

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The motions of the 60 most flexible amino acids of the antibody, during the 20 nanoseconds (10x2ns) of simulation, are then compared to the motions of the corresponding amino acids of 49 homology models of human antibody germ lines, for each of which ten molecular dynamic simulations (10x2 ns) have been run using the same protocol. The 60 most flexible amino acids exclude the antigen complementarity determining region (CDR) and its immediate vicinity. The 49 human antibody germ line models were built by systematically combining the 7 most frequent human light chains (vk1, vk2, vk3, vk4, vlamba1, vlamba2, vlamba3) and the 7 most frequent human heavy chains (vh1a, vh1b, vh2, vh3, vh4, vh5, vh6) (Nucleic Acids Research, 2005, Vol. 33, Database issue D593-D597).

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The similarity of the antibody to be humanized to the 49 human germ line models is quantified by sampling the positions of specific atoms of the 60 flexible amino acids of an antibody, over the course of the ten molecular dynamic simulations, by means

of a unique tridimensional cubic grid which has a 1Å resolution. This is referred to as quadridimensional similarity. The tridimensional grid used is made of 445 740 points and is initialized using the tridimensional structure of the human antibody corresponding to the PDB code 8FAB. The 8FAB structure is also used to position all the conformations of an antibody to be sampled in the tridimensional grid. For this purpose, the medoid conformation of the molecular dynamic of the antibody is superposed onto the 8FAB structure. This superposition consists of aligning the moments of inertia of the two conformations, followed by the optimization of the scalar distances between the alpha carbon atoms of both conformations. All the remaining conformations of the molecular dynamic of the antibody are superposed onto the medoid conformation using the same method.

Two types of sampling are performed, which result in two similarities (electrostatic similarity and lipophilic similarity), for a pair of antibodies being compared. These two similarities are then added to obtain the total similarity. The first sampling, the electrostatic sampling, considers all atoms of the amino acid side chain. The value in one point, x, of the grid is obtained by applying, to the atoms of the amino acid side chain, a tridimensional Gaussian function f(x) weighted with the atomic partial charge as described in the Amber99 force field (Cieplak, J., and al.; J. Comp. Chem. 2001, 22:1048-1057). The f(x) function is applied on the 3 Cartesian coordinate axes and

corresponds to the following formula: $f(x) = \left(s\sqrt{2\pi}\right)^{-3} \times \exp\left(\frac{-(x-u)^2}{2s^2}\right)$, with x and u

being, respectively, the Cartesian coordinates of a grid point x and of a sampled atom, and $s = r/1.6$ (r = covalence radius of the atom). The sampling is repeated for all conformations of the amino acid and the obtained results are averaged at all points x of the tridimensional grid. The second sampling, the lipophilic sampling,

considers only the lipophilic atoms of the amino acid side chain. The value at one point, x, of the grid is calculated with the same Gaussian function f(x) without weighting. As a result, the two ensembles of conformations from the molecular dynamic simulations, of the two antibodies being compared, are sampled by the same tridimensional grid. The electrostatic similarity (sim-elec) between antibody a and antibody b is measured with the following formula:

$$\text{sim-elec} = \frac{\sum_{i=1}^{445740} \left(\left| x_i^a + x_i^b \right| - \left| x_i^a - x_i^b \right| \right)}{\sum_{i=1}^{445740} \left(\left| x_i^a + x_i^b \right| \right)}$$

The lipophilic similarity is calculated with the

same formula applied to the data generated by the lipophilic sampling previously described.

The human germ line model vlamba2-vh2 thus displays the highest quadridimensional similarity (total similarity = 58%) of these 60 flexible amino acids with respect to the flexible amino acids of the murine antibody 40-12. The human germ line model vlamba2-vh2 has thus been used to humanize the antibody to be humanized, while focusing on the 45 flexible amino acids. In order to determine the mutations to be made, the tridimensional structure of the model of the murine antibody 40-12 is superposed on that of the model derived from the germ lines showing the highest similarity, with the positions of the alpha carbons of the amino acids being optimized. The amino acids identified as flexible are mutated with the corresponding amino acids in the sequence of the model showing the highest similarity.

The unwanted sequence motifs considered are the following: Aspartate-Proline (peptide bond labile in acidic medium), Asparagine-X-Serine/Threonine (glycosylation site, X=any amino acid except Proline), Aspartate-Glycine/Serine/Threonine (potential formation of succinimide/isoaspartate in the flexible zones), Asparagine-Glycine/Histidine/Serine/Alanine/Cysteine (exposed deamidation sites), Methionine (oxidation in the exposed zones). The humanized sequences thus obtained are finally compared, by means of the BLAST sequence comparison algorithm, with the sequences of the IEDB database (<http://www.immuneepitope.org/> The immune epitope database and analysis resource: from vision to blueprint. PLoS Biol. 2005 Mar;3(3):e91) so as to be sure that the sequences do not contain any epitopes known to be recognized by B and T lymphocytes. If the sequence contains residues which have unwanted sequences, they are then also modified. If the composite sequence contains a known epitope listed in the IEDB, another germ line structure template showing a high similarity is then used as model.

More advantageously, the antibody according to the invention comprises sequences having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 30 or the sequence SEQ ID No. 32 are used, in combination with the sequences having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 34, the sequence SEQ ID No. 36 or the sequence SEQ ID No. 38.

In one embodiment, the antibody according to the invention comprises variable light chains of sequence SEQ ID No. 30 and variable heavy chains of sequence SEQ ID No. 34.

- 5 In another embodiment, the antibody comprises variable light chains of sequence SEQ ID No. 32 and variable heavy chains of sequence SEQ ID No. 38.

In another embodiment, the antibody comprises variable light chains of sequence SEQ ID No. 30 and variable heavy chains of sequence SEQ ID No. 36.

- 10 In another embodiment, the antibody comprises variable light chains of sequence SEQ ID No. 32 and variable heavy chains of sequence SEQ ID No. 34.

In another embodiment, the antibody comprises variable light chains of sequence SEQ ID No. 32 and variable heavy chains of sequence SEQ ID No. 36.

- 15 In another embodiment, the antibody comprises variable light chains of sequence SEQ ID No. 30 and variable heavy chains of sequence SEQ ID No. 38.

- A subject of the present invention is also FGF-R4-specific human antagonist antibodies. Such antibodies can be obtained by phage display according to methods known to those skilled in the art (McCafferty J. and *al*, 1990; Hoogenboom, HR and
20 *al*, 2005). Other technologies are available for the preparation of human antibodies, such as the XenoMouse technology described in US patent 5,939,598.

- In one particular embodiment, the FGF-R4 receptor-specific antagonist antibody is a human antibody of which the heavy chain variable regions comprise a sequence
25 having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 76, 86, 96 or 106.

- In another embodiment, the FGF-R4 receptor-specific antagonist antibody is a human antibody of which the light chain variable regions comprise a sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 71,
30 81, 91 or 101.

A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising a heavy chain comprising a variable region encoded by a nucleotide sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 77, 87, 97 or 107.

A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising a light chain comprising a variable region encoded by a nucleotide sequence having at least 80%, 90%, 95% or 99% identity with the sequence SEQ ID No. 72, 82, 92 or 102.

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A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising sequences encoded by the nucleotide sequences SEQ ID Nos. 71 and 76 or the nucleotide sequences SEQ ID Nos. 81 and 86 or the nucleotide sequences SEQ ID Nos. 91 and 96 or the nucleotide sequences SEQ ID

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Nos. 101 and 106.

A subject of the present invention is also an FGF-R4 receptor-specific human antagonist antibody comprising the polypeptide sequences SEQ ID Nos. 72 and 77 or the polypeptide sequences SEQ ID Nos. 82 and 87 or the polypeptide sequences SEQ ID Nos. 92 and 97 or the polypeptide sequences SEQ ID Nos. 102 and 107.

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Particularly preferably, an FGF-R4 receptor-specific human antagonist antibody comprises the polypeptide sequences SEQ ID Nos. 82 and 87.

The amino acid sequences thus modified can also be modified by means of post-translational modifications during the production in the mammalian cell. In particular,

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the use of stable lines deficient in fucose biosynthesis can make it possible to produce monoclonal antibodies in which the N-glycan of the Fc (position N297) partially or completely lacks fucose and makes it possible to increase the ADCC effector effect (Kanda and *al.*, 2006, *Biotechnol. Bioeng.* 94:680-688 and Ripka and *al.*, 1986 *Arch Biochem Bioph* 249: 533-545).

25

In another embodiment of the invention, the FGF-R4-specific antagonist is a conjugated antibody.

The antibodies may be conjugated to a cytotoxic agent. The term "cytotoxic agent" denotes herein a substance which reduces or blocks the function or the growth of the

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cells, or causes destruction of the cells.

In one embodiment, the antibody or a binding fragment thereof can be conjugated to a drug, such as a maytansinoid, so as to form a "prodrug" which has cytotoxicity with respect to the cells expressing the antigen.

The cytotoxic agent of the present invention may be any compound which results in the death of a cell, or induces the death of a cell, or decreases cell viability in various ways. The preferred cytotoxic agents include, for example, maytansinoids and maytansinoid analogues, taxoids, CC-1065 and CC-1065 analogues, dolastatin and dolastatin analogues, defined above. These cytotoxic agents are conjugated to antibodies, antibody fragments, functional equivalents, improved antibodies and analogues thereof, as described in the present application.

The conjugated antibodies may be prepared by *in vitro* methods. A linker group is used to link a drug or a prodrug to the antibody. Suitable linker groups are well known to those skilled in the art and include, in particular, disulphide groups, thioether groups, labile acid groups, photolabile groups, labile peptidase groups and labile esterase groups. Preferred linker groups are disulphide groups and thioether groups. For example, a conjugate can be constructed by using a disulphide exchange reaction or by forming a thioether bridge between the antibody and the drug or prodrug.

Compounds such as: methotrexate, daunorubicin, vincristine, vinblastine, melphalan, mitomycin C, chlorambucil, calicheamicin, tubulysin and tubulysin analogues, duocarmycin and duocarmycin analogues, dolastatin and dolastatin analogues, are also suitable for the preparation of conjugates of the present invention. The molecules may also be linked to the antibody molecules via an intermediate molecule such as serum albumin. Doxorubicin and doxorubicin compounds, as described, for example, in patent application US 09/740991, may also be useful cytotoxic agents.

The antibodies which are the subject of the present invention may be combined with a cytotoxic molecule or compound. They may also be combined with an anti-angiogenic compound that acts on other angiogenic pathways.

The expression "cells expressing FGF-R4" refers to any eukaryotic cell, especially mammalian cell, and in particular human cell, which expresses an FGF-R4 receptor in its native form or in a mutated form. The FGF-R4 may also be in its whole form or in a truncated form comprising, for example, the extracellular domain of FGR-R4, and in particular the D2-D3 domains. The FGF-R4 may also be recombined in a chimeric form.

The compounds of the invention may be formulated in pharmaceutical compositions for the purpose of topical, oral, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, etc., administration. Preferably, the pharmaceutical compositions contain carriers that are pharmaceutically acceptable for an injectable formulation. They may in particular be sterile, isotonic, saline solutions (monosodium phosphate, disodium phosphate, sodium chloride, potassium chloride, calcium chloride or magnesium chloride etc., or mixtures of such salts), or dry, in particular lyophilized, compositions which by means of the addition, as appropriate, of sterilized water or physiological saline, can form injectable solutes.

The pathologies targeted may be all diseases related to angiogenesis, whether said angiogenesis is tumoral or non-tumoral.

The pathologies targeted may be cancer (with the use of the invention as an inhibitor of tumour angiogenesis), in particular liver cancer, colon cancer, breast cancer, lung cancer, prostate cancer, pancreatic cancer or skin cancer, or else pathologies for which a dysregulation of angiogenesis is described, such as: age-related macular degeneration or ARMD, inflammatory diseases such as rheumatoid arthritis, osteoarthritis, colitis, ulcers or any inflammatory disease of the intestines, atherosclerosis or else in the treatment of obesity.

The anti-FGF-R4 antibodies may also be used for treating cancer, in particular hepatocarcinomas and other hepatic cancers, and pancreatic cancer as an inhibitor having an action directly on tumour growth.

The present invention is illustrated, without however being limited, by the examples which follow.

Description of the figures

Figures 1A and 1B: *In vitro* (Fig. 1A), human endothelial cells of HUVEC type are capable of forming a network of pseudotubules, known as angiogenesis. This network is stimulated by the addition of 1 ng/ml of FGF2. This induction can also be obtained by adding 10 ng/ml of FGF19, which is a ligand specific for FGF-R4,

whereas 10 ng/ml of FGF4 (ligand which does not activate FGF-R4) are not capable of stimulating angiogenesis. In the same way, *in vivo* (Fig. 1B) in a murine model of induction of angiogenesis in a sponge implant on the back of the mouse, FGF2 is capable of inducing the recruitment of functional neovessels to the sponge, which is
5 characterized by an increase in the haemoglobin content of these sponges in comparison with the control. FGF19 is also capable of inducing this angiogenesis in the sponge.

Figure 2A: Map of the plasmid pXL4614 enabling the expression of hFGFR4-Histag
10 (SEQ ID No. 40).

Figure 2B: Map of the plasmid pXL4613 enabling the expression of hFGFR4-Streptag (SEQ ID No. 69).

15 **Figure 3:** Map of the plasmid pXL4615 enabling the expression of hFGFR4(D2,D3)-Histag (SEQ ID No. 42).

Figure 4: Map of the plasmid pXL4621 enabling the expression of mFGFR4-Histag (SEQ ID No. 44).
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Figure 5: Map of the plasmid pXL4328 enabling the expression of hFGFR1-Fc (of sequence SEQ ID No. 46).

Figure 6: Map of the plasmid pXL4327 enabling the expression of hFGFR2-Fc (of
25 sequence SEQ ID No. 48).

Figure 7: ELISA plates are coated with the 4 human FGF receptors. The ability of the anti-FGFR4 antibodies 40-12 and 64-12 to recognize these various FGF-Rs is measured by ELISA assay. Clone 40-12 (black histogram) is specific for FGF-R4.
30 Clone 64-12 (grey histogram) recognizes, in addition, FGF-R3 very weakly.

Figures 8A and 8B: The active antagonist antibody 40-12 and its inactive control 64-12 have no effect per se on basal angiogenesis. On the other hand, at the dose of 30 µg/ml (approximately 200 nM), the anti-FGFR4 monoclonal antibody 40-12 is

capable of inhibiting the FGF2-induced angiogenesis of HUVEC cells, whereas the control antibody 64-12 is not capable of doing so (Fig. 8A).

FGF2 labelled with an AlexaFluor® 488 nm is capable of binding to the FGF-R4 expressed by 300-19 cells (white histogram). This interaction can be dissociated by
5 unlabelled FGF2 (black histograms) or by the anti-FGFR4 antibody 40-12 (dark grey histograms), whereas the control antibody 64-12 is not capable of doing so (light grey histograms) (Fig. 8B).

Figure 8C and 8D: Effect of the anti-FGFR4 antibodies derived from clones 8, 31,
10 33 and 36, at 10 µg/ml, on the *in vitro* angiogenesis induced by 3 ng/ml of FGF-2. Clones 8 (Fig. 8C) and 31, 33 and 36 (Fig. 8D) inhibit the FGF-2-induced angiogenesis of HUVEC cells.

Figures 9A and 9B: Hep3b human hepatocarcinoma cells are stimulated with
15 FGF19 at 30 ng/ml. This stimulation induces FGF-R4-specific cell signalling, resulting in synthesis of the cFos and JunB proteins and in the phosphorylation of Erk1/2, observed by Western blotting (Fig. 9A). Each band is then quantified. This quantification is represented in the form of a histogram (Fig. 9B). The antibody 40-12 at 100 µg/ml completely inhibits the induction of the FGF-R4-specific cell signalling,
20 whereas the control antibody has no effect. Specifically, the antibody 40-12 completely blocks the synthesis of JunB and of cFos and also the phosphorylation of Erk1/2 induced by FGF19 after a stimulation of 3 h.

Figure 9C: The inhibitory effect of the anti-FGFR4 antibody 40-12 on the
25 phosphorylation of Erk1/2 induced in the Hep3b cells by FGF-19 (30 ng/ml) is confirmed by means of the anti-phosphoErk1/2 ELISA. The antibody 40-12 is also capable of inhibiting the phosphorylation of Erk1/2 in Hep3b cells stimulated with FGF-2 (1 ng/ml) or with serum (FCS) at 10%.

Figure 9D: Percentage inhibition of Erk1/2 phosphorylation induced by FGF-19
30 (30 ng/ml) obtained by ELISA on Hep3b cells using the antibodies derived from clones 8, 31, 33 and 36.

Figures 10A and 10B: The proliferation of Hep3b cells can be stimulated by adding
35 serum (Fig. 10A) or FGF19 (Fig. 10B). The induction with serum is partially inhibited

by the antibody 40-12 at 100 µg/ml, whereas the control antibody has no effect (Fig. 10A). The proliferation induced by FGF19 is completely blocked with 10 µg/ml of anti-FGFR4 antibody 40-12, whereas at the same dose, the control antibody is not capable of doing so (Fig. 10B).

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Figures 11A to 11D: The anti-FGFR4 antibody 40-12 is capable of reducing the development of pancreatic tumors in a RipTag murine model by inhibiting tumour angiogenesis: The Rip1-Tag2 model is a murine model in which transgenic mice expressing the SV40 T antigen in the insulin-producing β cells of the pancreatic islets (Hanahan D. Nature, 1985, 9-15:115-22.). This T antigen is expressed during embryonic development of the pancreas up to 4 to 5 weeks of life, without apparent effect. Some of the pancreatic islets expressing the T antigen then progress, during the next 5 weeks, towards the formation of angiogenic islets associated with activation of the vasculature and then towards the development of small tumours of adenoma type. A few weeks later, some adenomas develop, so as to form invasive carcinomas (Fig. 11A).

These Rip1-Tag2 mice are treated subcutaneously once a week, between weeks 10 and 13, at the dose of 25 mg/kg, with the antibody 40-12 or with the control antibody. After 13 weeks, the mice are sacrificed. The tumour volume and also the number of tumours per pancreas and the vascular density are determined. The treatment with the anti-FGFR4 antibody 40-12 makes it possible to significantly reduce the tumour volume by 55%, whereas the control antibody shows no effect (Fig. 11B). The antibody 40-12 also makes it possible to reduce by 34% the number of tumours per pancreas, compared with the control (Fig. 11C). This reduction in tumour volume is accompanied by a reduction in the vascular density, whether in terms of the number of small, medium or large vessels (Fig. 11D).

Figure 12: The ability of the antibodies 40-12 and 64-12 to recognize the complete extracellular domain of human or murine FGF-R4, and also the extracellular domain of FGF-R4 deleted of its D1 domain, is measured by ELISA. Clone 40-12 is capable of binding equally with the 3 FGF-R4 constructs, whereas clone 64-12 recognizes the murine form of FGF-R4 less well.

Figures 13A to 13C: The antagonistic effect of the anti-FGFR4 antibody clone 40-12

on FGF2/FGF-R4 binding is measured by means of competition binding experiments with FGF2 labelled with an AlexaFluor® 488 nm. Clone 40-12 is capable of blocking the binding of human (Fig. 13A), murine (Fig. 13B) and rat (Fig. 13C) FGF2 on murine 300-19 cells transfected with cDNA encoding the human, murine or rat forms of the FGF-R4 receptor, with the same effectiveness (3500, 4110 and 3940 ng/ml, i.e. 23, 27 and 26 nM for the human, murine or rat complexes, respectively).

Figure 14A: Map of the plasmid pXL4794 enabling the expression of hFGFR4_D1: Fc.

Figure 14B: Amino acid sequence of the hFGFR4_D1: Fc protein secreted in the HEK293 line transfected with the plasmid pXL4794.

Figure 15A: Map of the plasmid pXL4796 enabling the expression of hFGFR4_D2: Fc.

Figure 15B: Amino acid sequence of the hFGFR4_D2: Fc protein secreted in the HEK293 line transfected with the plasmid pXL4796.

Figure 16A: Map of the plasmid pXL4799 enabling the expression of hFGFR4_D3: Fc.

Figure 16B: Amino acid sequence of the hFGFR4_D3: Fc protein secreted in the HEK293 line transfected with the plasmid pXL4799.

EXAMPLES:

Example 1: Demonstration of the role of FGF-R4 in the control of angiogenesis

In order to demonstrate the role of FGF-R4 in the control of angiogenesis, *in vitro* angiogenesis experiments were carried out with human endothelial cells of HUVEC type stimulated with several FGFs: FGF2, a ligand which activates most of the FGF receptors; FGF19, a ligand which specifically activates FGF-R4; and FGF4, a ligand which does not activate FGF-R4.

To do this, gels were prepared by distributing, into each well of a chamberslide

(Biocoat Cellware collagen, type I, 8-well culture slides: Becton dickinson 354630), 160 μ l of matrigel diluted to 1/6 (Growth factor reduced Matrigel: Becton dickinson 356230) in collagen (rat Tail collagen, type I: Becton dickinson 354236). The gels are maintained at 37°C for 1 hour so as to enable them to polymerize. Next, the human

5 vein endothelial cells (HUVEC ref: C-12200 – Promocell) were seeded at 15×10^3 cells/well in 400 μ l of EBM medium (Clonetics C3121) + 2% FBS + 10 μ g/ml of hEGF. This protocol can be adapted to 96-well plates: 60 μ l per well of 96-well plates (Biocoat collagenI cellware, Becton Dickinson 354407). The matrix is prepared by mixing 1/3 of matrigel, 1 mg/ml final concentration of collagen, NaOH

10 (0.026x the volume of collagen in μ l), 1x PBS, the volume then being adjusted with water. The endothelial cells are stimulated with 1 ng/ml of FGF2 (R&D, 133-FB-025) or 10 ng/ml of FGF4 (R&D, 235-F4-025) or of FGF19 (R&D, 969-FG-025) for 24 h at 37°C in the presence of 5% CO₂. After 24 hours, the length of the network of microtubules formed is measured using a computer-assisted image analysis system

15 (Imagenia Biocom, Courtaboeuf, France) and the total length of the pseudotubules in each well is determined. The mean of the total length of the microcapillary network is calculated in μ m for each condition corresponding to the mean of 6 replicates.

The stimulation with FGF2 or FGF19 enables the induction of the formation of new tubules, whereas FGF4 has no effect (Fig. 1A). These results show that the specific

20 activation of FGF-R4 makes it possible to induce the formation of neovessels and therefore to conclude that FGF-R4 controls angiogenesis *in vitro*.

The *in vivo* correlation with the *in vitro* data was obtained using the model of angiogenesis induction *in vivo* in cellulose implants in mice. This model is an

25 adaptation of the model described by Andrade and *al.* (*Microvascular Research*, 1997, 54, 253-61).

The animals, inbred white BALB/c J mice, are anaesthetized with a xylazine (Rompun®, 10mg/kg)/ketamine (Imalgene 1000, 100 mg/kg) mixture given intraperitoneally. The back of the animal is shaved and disinfected with

30 Hexomedine®. A pocket of air is created subcutaneously on the back of the mouse by injection of 5 ml of sterile air. An incision of approximately 2 cm is made on the upper back of the animal in order to introduce a sterile cellulose implant (disc 1 cm in diameter, 2 mm thick, Cellspan® ref 0501) impregnated with 50 μ l of sterile solution containing the protein or the product to be tested. The incision is then sutured and

cleaned with Hexomedine®. During the days following the implantation of the implant, the mice received, in the implant, the protein or the product by means of an injection through the skin (50 µl/implant/day) under gas anaesthesia (5% isoflurane (Aerrane®, Baxter)).

- 5 Seven days after the implantation of the sponge, the mice are sacrificed by means of a lethal dose of sodium pentobarbital (CEVA santé animale), administered intraperitoneally. The skin is then cut, approximately 1 cm around the sponge, avoiding the scar, in order to free the skin and the sponge. The sponge is then cut up into several pieces and placed in a Ribolyser® tube containing 1 ml of lysis buffer
10 (Cell Death Detection ELISA, Roche). The tubes are shaken 4 consecutive times, for 20 sec, force 4, in a cell homogenizer (FastPrep® FP 120). The tubes are then centrifuged for 10 min at 2000 g at 20°C and the supernatants are frozen at -20°C while awaiting the haemoglobin assay.

- On the day of the assay, the tubes are again centrifuged after thawing, and the
15 haemoglobin concentration is measured with the Drabkin reagent (Sigma, volume for volume) by reading on a spectrophotometer at 405 nm against a standard range of bovine haemoglobin (Sigma). The haemoglobin concentration in each sample is expressed in mg/ml according to the polynomial regression performed on the basis of the standard range. The results are expressed in mean value ($\pm$ sem) for each
20 group. The differences between the groups are tested with an ANOVA followed by a Dunnett's test on the square root of the values.

- In this model, FGF19 at 50 ng per site and 5 re-injections is capable of significantly inducing colonization of the sponge by newly formed mature vessels, with the same effectiveness as FGF2 at 5 ng per site. The presence of functional blood vessels in
25 the sponge is demonstrated by the presence of haemoglobin (Fig. 1B). These results show that the specific activation of FGF-R4 enables the recruitment of functional blood vessels, indicating that FGF-R4 also controls angiogenesis *in vivo*.

Example 2: Description of the FGFR proteins used as immunogen and antigen

- 30 FGFR growth factor receptors, and in particular the extracellular domains of FGF-R1, FGF-R2, FGF-R3, FGF-R4, are fused to a tag (Histag) or to the immunoglobulin Fc domain.

The cDNA encoding the extracellular domain of human FGF-R4 corresponds to the protein described in SwissProt FGF-R4_HUMAN position 1-365 with the L136P

mutation. It was cloned into the eukaryotic expression vector pXL4614 represented in Figure 2, in order to express a protein containing a Histag in the C-terminal position in the extracellular domain.

5 The proteins named hFGFR4-Histag, of sequence SEQ ID No. 40, were produced by transient transfection in the HEK293 EBNA line (Invitrogen) using the plasmid pXL4614 and the helper plasmids pXL4544 and pXL4551 which enable the expression of two N-glycan glycosylation enzymes, i.e. α -2,3-sialyltransferase and β -1,4-galactosyltransferase, as described in application WO2008/065543.

10 The hFGFR4-Histag protein expressed in the HEK293 EBNA cell culture supernatant was purified by chromatography on an Ni-chelating sepharose column (Amersham Biosciences; ref. 17-0575-01), elution being carried out in an imidazole buffer, and then formulated in PBS buffer (Invitrogen; ref. 14190-094). The analysis of the monosaccharide composition and the quantification of the sialic acids of the
15 N-glycans, as described by Saddic and *al.* 2002. (Methods Mol. Biol. 194:23-36 and Anumula and *al.* 1998. Glycobiology 8:685-694), made it possible to demonstrate that the protein was very highly sialylated (91%). Consequently, the protein had all the characteristics for having sufficient pharmacokinetic properties.

In a comparable manner, the hFGFR4-Streptag protein (SEQ ID No. 69) was purified
20 by chromatography on a Strep-Tactin Superflow column (IBA; ref. 2-1206), elution being carried out in a desthiobiotin buffer, and then formulated in PBS buffer.

The hFGFR4(D2,D3)-Histag protein corresponds to the sequence SEQ ID No. 42. The cDNA was cloned into the eukaryotic expression plasmid pXL4615 represented
25 in Figure 3, and the protein was produced and purified under conditions comparable to the hFGFR4-Histag protein.

The cDNA encoding the mFGFR4-Histag protein (SEQ ID No. 43) was cloned into the eukaryotic expression plasmid pXL4621 represented in Figure 4, and the protein was produced and purified under conditions comparable to the hFGFR4-Histag
30 protein.

The hFGFR1-Fc protein (SEQ ID No. 46) contains the extracellular domain of human FGF-R1 IIIc fused, in the C-terminal position, to the Fc domain of human IgG1. The cDNA was cloned into the eukaryotic expression plasmid pXL4728 represented in

Figure 5, and the protein was produced under conditions comparable to the hFGFR4-Histag protein and then purified by chromatography on a protein G Sepharose affinity column (Amersham Biosciences), elution being carried out in 100 mM glycine/HCl buffer, pH 2.7, and then formulated in PBS buffer.

- 5 The hFGFR2-Fc protein, of sequence SEQ ID No. 48, contains the extracellular domain of human FGF-R2 IIIc fused, in the C-terminal position, to the Fc domain of human IgG1. The cDNA was cloned into the eukaryotic expression plasmid pXL4327 represented in Figure 6, and the protein was produced and then purified under conditions comparable to the hFGFR1-Fc protein.
- 10 The hFGFR3-Fc protein is a protein which fuses the extracellular domain of human FGF-R3 IIIc to the Fc domain of human IgG1, and was obtained from R&D Systems (ref: 760-FR).

The hFGFR4-Fc protein is a protein which fuses the extracellular domain of human FGF-R4 to the Fc domain of human IgG1, and was obtained from R&D Systems

15 (ref: 685-FR).

Various subdomains of the extracellular portion of the hFGFR4 protein were fused to the Fc domain of human IgG1. The D1 subdomain is contained in the construct SABVA4794 (SEQ ID No. 112 and Figs 14A and 14B). The D2 subdomain is

20 contained in the construct SABVA4796 (SEQ ID No. 114 and Figs 15A and 15B). The D3 subdomain is contained in the construct SABVA4799 (SEQ ID No. 116 and Figs 16A and 16B). These three subdomains extend respectively from positions 1 to 179 for SABVA4794, 1 to 32 plus 145 to 242 for SABVA4796, and 1 to 32 plus 228 to 360 for SABVA4799 (positions described in SwissProt FGF-R4_HUMAN). These

25 were produced using the plasmids pXL4794 (coding sequence SEQ ID No. 111), pXL4796 (coding sequence SEQ ID No. 113) and pXL4799 (coding sequence SEQ ID No. 115) under conditions comparable to the FGFR1-Fc protein.

Example 3: Generation and screening of anti-FGF-R4 monoclonal antibodies

30

A – Antibodies obtained by immunization

The monoclonal antibodies were obtained by immunization with the hFGFR4-Histag immunogen in five BALB/cJ mice (Charles River), 6 to 8 weeks old, each immunized with a total of 24 µg of hFGFR4-Histag by the RIMMS method described by Kilpatrick

and *al.* (1997. Hybridoma 16: 381389) and the fusion protocol described in ClonaCell™- HY Hybridoma Cloning Kit (StemCell Technologies; ref 03800).

- Two days after the final injection, the mice were sacrificed and the lymph nodes were
- 5 fused with P3X63-AG8.653 myeloma cells (ATCC, CRL-1580) in a 5:1 ratio in the presence of polyethylene glycol (ClonaCell™-HY ref. 03806). The cell suspension was distributed aseptically into Petri dishes incubated at 37°C in the presence of 5% CO₂. The colonies that had appeared after 12 days of incubation were isolated and cultured in medium E (ClonaCell™-HY; ref. 03805) in 96-well plates.
- 10 The primary screening of monoclonal antibodies obtained by immunization with hFGFR4-Histag was carried out by ELISA assay using hFGFR4-Streptag as capture antigen. The capture antigen was bound to Immulon-4 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). The hybridoma culture supernatants were subsequently added and then detection was carried out using the peroxidase-
- 15 conjugated anti-mouse IgG rabbit antibody (Sigma; ref. A9044-dilution to 1:50 000). The revealing was carried out with the TMB-H₂O₂ substrate (Interchim; ref UP664780) and the measurements were carried out with the plate reader at 450 nm. Among the 444 hybridomas tested, 129 were positive by ELISA assay with the hFGFR4-Streptag antigen, and 120 of these hybridomas were also positive with the
- 20 hFGFR4-Fc dimer protein.

- A secondary screen was carried out, in order to select only the FGF-R4-specific antibodies, by ELISA assay using as capture antigen the hFGFR4-Streptag protein, and then with the hFGFR1-Fc, hFGFR2-Fc and hFGFR3-Fc proteins described in
- 25 Example 2. The capture antigen was bound to Immulon-4 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). The hybridoma culture supernatants were subsequently added and then detection was carried out using the peroxidase-conjugated anti-mouse IgG rabbit antibody (Sigma; ref. A9044-dilution to 1:50 000). The revealing was carried out with the TMB-H₂O₂ substrate (Interchim; ref
- 30 UP664780) and the measurements were carried out with the plate reader at 450 nm. Among the 129 hybridomas that tested positive by ELISA assay with the antigen, 84 hybridomas were positive with hFGFR4-Streptag and had no affinity for either hFGFR1-Fc, hFGFR2-Fc or hFGFR3-Fc. 39 hybridomas were conserved, as a function of their growth and their morphology. Their isotype was determined using

the SEROTEC kit (ref. MMT1); 95% were IgG1s.

A tertiary screen was carried out on a test for FGF2-induced proliferation of Baf/3 modified cells, in order to characterize the inhibition by the anti-FGFR4 antibodies.

- 5 The murine hybridomas expressing the anti-FGFR4 antagonist antibodies were cloned by limiting dilution. Using the hybridoma cells cultured in the exponential phase, the coding sequence (cDNA) was determined after extraction of the mRNA using the Oligotex kit (Qiagen; ref 72022); production and amplification of the cDNA by the RACE-RT method with the Gene Racer kit, the SuperScript III reverse
10 transcriptase (Invitrogen; ref L1500) and the primers described in Table 2 below; amplification of the cDNA fragments using the Phusion polymerase (Finnzymes; ref. F-530S), the primers and the temperature conditions described in Table 2. The amplified fragments containing the coding regions for VH (variable region of the heavy chain HC) or VL (variable region of the light chain LC) were cloned into the
15 pGEM-T Easy vector from Promega; ref A137A, and the inserts of the plasmids obtained were sequenced, such that the coding sequence of each variable domain was analysed in the 5'-3' and 3'-5' direction on at least 6 plasmids corresponding to the anti-FGFR4 antibody 40-12 and the anti-FGFR4 antibody 64-12. The analyses of sequence, contigs and alignments were carried out using the software available on
20 Vector NTI (Invitrogen).

The plasmids containing the consensus sequences encoding the variable regions of the anti-FGFR4 antibodies were conserved. The plasmid pXL4691 contains the sequence encoding the VH of sequence SEQ ID No. 5 of the anti-FGFR4 antibody
25 40-12, and the plasmid pXL4693 contains the sequence encoding the VH of sequence SEQ ID No. 19 of the anti-FGFR4 antibody 64-12, as shown in Table 2 below.

The plasmid pXL4690 contains the nucleotide sequence SEQ ID No. 7 encoding the VL of sequence SEQ ID No. 8 of the anti-FGFR4 antibody 40-12, and the plasmid
30 pXL4692 contains the nucleotide sequence SEQ ID No. 21 encoding the VL of sequence SEQ ID No. 22 of the anti-FGFR4 antibody 64-12, as shown in Table 2 below.

Table 2 – Operating conditions and analysis of the reverse transcriptase and PCR

reactions – identification of the plasmids pXL4690 to pXL4693.

Anti-FGFR4	40-12	64-12
RT reaction Temperature Primers	55°C SEQ ID No. 64 (HC) SEQ ID No. 65 (LC)	55°C SEQ ID No. 64 (HC) SEQ ID No. 66 & SEQ ID No. 67 (LC)
5' Primer-GeneRacer (SEQ ID No. 63)	5'-CGACTGGAGCACGAGGACACTGA-3'	
3' Primer-internal to murine hinge (SEQ ID No. 64)	5'-TATGCAAGGCTTACAACCACA-3'	
3' Primer-internal to murine C κ (SEQ ID No. 65)	5'-CTCATTCTGTT GAAGCTCTT GAC-3'	
3' Primers-internal to murine C λ (SEQ ID No. 66 and SEQ ID No. 67)		5'- ACACTCAGCACGGG ACAACTCTTCTC-3' 5'- ACACTCTGCAGGAG ACAGACTCTTTTC-3'
HC PCR: Temperature Primers	55°C SEQ ID No. 63 - SEQ ID No. 64	55°C SEQ ID No. 63 – SEQ ID No. 64
Sequence of the cloned PCR products (VH)	9 clones have the same VH sequence and a CH1 sequence identical to that of mCH1-	6 clones have the same VH sequence and a CH1 sequence identical to that of mCH1
Plasmid containing VH	pXL4691	pXL4693
LC PCR: Temperature Primers	55°C SEQ ID No. 63 – SEQ ID No. 65	55°C SEQ ID No. 63 – SEQ ID No. 66 & 67
Sequence of the cloned PCR products (VL)	11 clones have the same VL sequence and a C κ sequence identical to mC κ	6 clones have the same VL sequence and a C λ sequence identical to mC λ
Plasmid containing VL	pXL4690	pXL4692

The amino acid sequences of the light and heavy variable regions, respectively, of the anti-FGFR4 antibody 64-12 and the anti-FGFR4 antibody 40-12 are different. The numbers of the sequences used, obtained and deduced are indicated in Table 5 7.

The antibodies 40-12 and 64-12 were produced in T500 flasks. The culture supernatant was harvested after 7 days. The anti-FGFR4 antibodies were affinity-purified on protein G and then dialysed against PBS, filtered sterile, and stored at 10 4°C.

The purified antagonist antibodies have a K_D of 6.5×10^{-9} M (anti-FGFR4 40-12) and 5.75×10^{-8} M (anti-FGFR4 64-12).

B – Antibody selected using the phage display method

15 The primary screening of monoclonal antibodies obtained by phage display with hFGFR4-Histag was carried out by ELISA assay using hFGFR4-Histag as capture antigen. The capture antigen was bound to Immulon-2 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). The culture supernatants from *E. coli* infected with the phages were subsequently added and then detection was carried out using the 20 peroxidase-conjugated anti-M13 mouse antibody (GE Healthcare; ref. 27-9421-01, dilution to 1:5000). The revealing was carried out with the TMB-H₂O₂ substrate (Interchim; ref UP664780) and the optical density (O.D.) measurements were carried out at 450 nm.

A secondary screen was carried out in order to select only the FGF-R4-specific 25 antibodies, by ELISA assay using as capture antigen the hFGFR4-Histag protein, and then with the hFGFR1-Fc, hFGFR2-Fc and hFGFR3-Fc proteins described in Example 2. The capture antigen was bound to Immulon-2 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). The culture supernatants from *E. coli* infected with the phages were subsequently added and then detection was carried out using 30 the peroxidase-conjugated anti-M13 mouse antibody (GE Healthcare; ref. 27-9421-01, dilution to 1:5000). The revealing was carried out with the TMB-H₂O₂ substrate (Interchim; ref UP664780) and the optical density (O.D.) measurements were carried out at 450 nm.

The FGF-R4-specific clones selected were sequenced and recloned into an

expression vector for transient transfection of HEK293 cells.

For this, in a first step, the regions encoding Fab, i.e. the light chain of the antibody, a bacterial ribosome binding site, and the heavy chain variable region of the antibody, are extracted from the phagemid by restriction and inserted into an IgG
5 expression plasmid for mammalian cells, downstream of a eukaryotic antibody signal sequence and upstream of the constant region of a human IgG1 heavy chain. In a second step, the region containing the bacterial ribosome binding site and the bacterial signal peptide for the heavy chain is exchanged against an IRES sequence and a eukaryotic signal sequence. The IgGs are expressed by transient transfection
10 of HEK293 cells. This process is described in detail in *T. Jostock et al., Journal of Immunological Methods* 289 (2004) 65–80.

An example of a human IgG1 constant region sequence that can be used in the present invention is the sequence SEQ ID No. 117.

15 A tertiary screen was carried out on a test for FGF2-induced proliferation of modified Baf/3 cells, described in Example 4, in order to characterize the inhibition by the anti-FGFR4 antibodies, using the culture supernatants from HEK293 cells transiently transfected with the antibody expression vectors. This screen made it possible to identify the antibodies of clones 8, 31, 33 and 36. The corresponding sequences are
20 described in Table 7.

Example 4: Establishment of the BaF/3 FGF-R4-hMpl murine clonal line and cell proliferation protocol

25 The extracellular and transmembrane domain of FGF-R4 was cloned, as a translational fusion with the intracellular domain of hMpl, into a mutated pEF6/V5-His A vector in order to obtain the presence, in the 5' position, of the HA tag in front of the chimeric FGF-R4-hMpl receptor.

30 Construction of the mutated pEF6A

The pEF6/V5-His A vector (Invitrogen, reference V961-20) was improved in order to integrate the MCS (multi cloning site) associated with the HA tag placed under the signal peptide of IgGk of pDisplay (Invitrogen, reference V660-20). To do this, the MCS associated with the HA tag and with its signal peptide were amplified by PCR

between the sense primer of sequence SEQ ID No. 51 and the reverse primer of sequence SEQ ID No. 52, making it possible to insert the KpnI restriction site in the 5' position and the XbaI restriction site in the 3' position. The PCR fragment was digested with the KpnI and XbaI enzymes and then cloned into the pEF6/V5-His A vector opened with the same enzymes. Finally, the first BamHI site of the MCS was replaced with the BsrGI site by digesting the newly formed vector with the KpnI and SpeI enzymes and inserting, between these sites, the primers of sequences SEQ ID No. 53 and SEQ ID No. 54, hybridized to one another and containing the BsrGI enzyme site. The vector obtained was called: pEF6mut-HA.

Construction of the pEF6mut-HA-FGF-R4-hMpl vector

The intracellular domain of Mpl was amplified in a vector pEF6/V5-His TOPO (Invitrogen, reference K9610-20) between the sense primer of sequence SEQ ID No. 55 allowing the insertion of the SacI digestion site and the reverse primer of sequence SEQ ID No. 56, commonly called revBGH. The PCR fragments generated were then digested with the SacI and NotI enzymes.

The extracellular and transmembrane domain of FGF-R4 was amplified using the pair of primers (sense: sequence SEQ ID No. 57; reverse: sequence SEQ ID No. 58). These primers make it possible to insert the BamHI enzymatic site in the 5' position and the SacI enzymatic site in the 3' position. The PCR fragment obtained was then digested with the BamHI and SacI enzymes.

The amplifications of DNA encoding hMpl and encoding FGF-R4 were then cloned simultaneously into the pEF6mut-HA vector opened with BamHI-NotI. The resulting construct was called "pEF6mut-HA FGF-R4 α IIIc-hMpl2". This construct was then improved by site-directed mutagenesis in order to change the transmembrane domain of FGF-R4 (protein sequence SEQ ID No. 59) for the sequence SEQ ID No. 60. To do this, the "QuickChange® Site-directed mutagenesis kit" (Clontech, reference 200518) was used with the sense primer of sequence SEQ ID No. 61 and the reverse primer of sequence SEQ ID No. 62. The new chimeric construct obtained was called pEF6mut-HA FGF-R4 α IIImut-hMpl2.

Creation of a stable line by transfection of the BaF/3 murine line with the FGF-R4 α IIImut-hMpl2 construct:

The "pEF6mut-HA FGF-R4alllcmut-hMpl2" construct was stably introduced, by electroporation, into the genome of the BaF/3 murine cells. The line obtained was selected in the presence of FGF2 at 20 ng/ml (R&D, reference 234-FSE-025) and of heparin at 100 ng/ml (Sigma, reference H3149). The transfected and selected line is then of clonal type.

Cell proliferation protocol with the BaF/3 FGFR4-hMpl cell line:

The BaF/3 FGFR4-hMpl cells were cultured and maintained in complete RPMI 1640 medium (Invitrogen; ref. 32404-014) (10% FCS (Hyclone; ref. SH30070.03), 2 mM glutamine, 1x MEM non essential amino acid (Gibco, ref 11140-035), 1x MEM sodium pyruvate (Gibco, ref 11360-039), supplemented with FGF2 at 20 ng/ml (R&D Systems, ref 234-FSE) and heparin at 3 ng/ml (Sigma, ref H3149). On day one, the cells are seeded at 0.4×10^6 cells/ml in complete RPMI 1640 medium supplemented with FGF2 at 20 ng/ml and with heparin at 3 ng/ml. The following day, 50 μ l of BaF/3 FGFR4-hMpl cell suspension in complete RPMI 1640 medium supplemented with FGF2 at 20 ng/ml and with heparin at 3 ng/ml, at 0.2×10^6 cells/ml, were dispensed into 96-well plates (Corvair, ref 214006), followed by 50 μ l of hybridoma supernatant containing the antibody to be tested. The plates were then placed at 37°C, 5% CO₂ for 24 to 30 h. For reading the cell proliferation, the amount of ATP was quantified by adding 100 μ l of Cell Titer Glo Luminescent Cell Viability Assay (Promega, ref G7571) and the luminescence was read using a luminometer.

The clones exhibiting, in this test, a signal 50% weaker than that of the complete RPMI 1640 medium containing the additives FGF2 at 20 ng/ml and heparin at 3 ng/ml were selected.

When the anti-FGFR4 antibodies, specific for FGF-R4, were incubated with the BaF/3-FGFR4-hMpl cells and with the following additives FGF2 at 20 ng/ml and heparin at 3 ng/ml, an antagonist effect was observed on cell proliferation. Among the 39 hybridomas tested, 14 are capable of inhibiting FGF-induced cell proliferation of BaF/3-FGFR4-hMpl cells in the presence of FGF2.

It was shown by ELISA (Fig. 12) that the anti-FGFR4 antagonist antibodies 40-12 and 64-12 had affinity for the murine protein mFGFR4 and human protein hFGFR4 (D2, D3).

Finally, a last screen was carried out by Surface Plasmon Resonance (BIAcore 2000) in order to determine the affinity constants of the anti-FGFR4 antibodies. The interaction between the FGF-R4 protein and the anti-FGFR4 antibody present in the hybridoma culture supernatant was analysed after having bound the anti-FGFR4 antibody to an anti-Fc antibody, itself bound to the CM chip. The kinetics are measured according to the protocol of Canziani et al 2004. Anal. Biochem. 325: 301-307.

Two antibodies among those having affinity constants of 10^{-8} to 10^{-9} M and dissociation rates of 10^{-3} to 10^{-5} s $^{-1}$ were selected. The characteristics of these antibodies are described in Table 1 below.

The reference method used to determine the K_D is Surface Plasmon Resonance (BIAcore).

Table 1A: Affinity and association/dissociation constants of the purified anti-FGFR4 antagonist antibodies 40-12 and 64-12

Anti-FGFR4	k_{on} (M $^{-1}$.s $^{-1}$)	k_{off} (s $^{-1}$)	K_D (M)
40-12	1.94×10^5	1.26×10^{-3}	6.50×10^{-9}
64-12	1.05×10^4	6.02×10^{-4}	5.75×10^{-8}

Table 1B: Kinetic parameters for binding of the anti-FGFR4 antibodies 8, 31, 33 and 36, measured by Surface Plasmon Resonance (BIAcore 3000):

	on h-FGFR4-Histag			on m-FGFR4-Histag		
	Kon (M $^{-1}$ s $^{-1}$)	Koff (s $^{-1}$)	KD (M)	Kon (M $^{-1}$ s $^{-1}$)	Koff (s $^{-1}$)	KD (M)
Clone 8	8.93×10^5	2.92×10^{-4}	3.27×10^{-10}	1.20×10^6	1.36×10^{-4}	1.15×10^{-10}
Clone 31	6.48×10^5	9.80×10^{-4}	1.52×10^{-9}	9.14×10^5	1.80×10^{-3}	1.97×10^{-9}
Clone 33	8.05×10^5	6.17×10^{-4}	7.71×10^{-10}	1.01×10^6	7.04×10^{-4}	6.92×10^{-10}
Clone 36	2.44×10^5	6.31×10^{-4}	2.62×10^{-9}	3.30×10^5	7.52×10^{-4}	2.28×10^{-9}

Example 5: Specificity of the anti-FGFR4 antibodies

A- Specificity of the anti-FGFR4 antibody 40-12 for FGF-R4

The specificity of each antibody is established by ELISA according to the protocol described in Example 4. In this way, the ability of each antibody to bind to each FGF-R is observed. This experiment clearly shows that the antibody 40-12 recognizes only FGF-R4 and is therefore specific for FGF-R4. The antibody 64-12 is capable of binding mainly to FGF-R4, but also weakly to FGF-R3 (Fig. 7).

B – Specificity of the anti-FGFR4 antibodies 8, 31, 33 and 36 for FGF-R4

- 10 The specificity of each antibody is established by ELISA according to the following protocol: suspensions of phages displaying, at their surface, the antibodies in the Fab format are generated by infection of *E. coli* bacteria. The capture antigens were bound to Immulon-2 enzyme-linked dishes (VWR Scientific Inc. Swedesboro, NJ). The phage suspensions were subsequently added and then
- 15 detection was carried out using the peroxidase-conjugated anti-M13 phage mouse antibody (GE Healthcare, ref. 27-9421-01, dilution to 1:5000). The revealing was carried out with the TMB-H₂O₂ substrate (Interchim; ref UP664780) and the optical density (OD) measurements were carried out at 450 nm. Table 2 summarizes the results obtained:
- 20 In this way, the ability of each antibody to bind to each FGF-R is observed. This experiment clearly shows that the antibodies 8, 31, 33, 36 recognize only FGF-R4 and are therefore specific for FGF-R4.

25 **Table 2:** Specificity of the anti-FGF-R4 antibodies derived from clones 8, 31, 33 and 36, established by ELISA (Signal = OD, 450 nm)

	h-FGFR4(D2,D3)-histag	h-FGFR1-Fc	h-FGFR2-Fc	h-FGFR3-Fc
Clone 8	2.55	0.05	0.00	0.00
Clone 31	2.52	0.00	0.00	0.01
Clone 33	2.73	0.00	0.00	-0.01
Clone 36	1.87	-0.01	-0.01	-0.02

30 **Example 6: Antagonistic effect of the antibody 40-12 and of the antibodies derived from clones 8, 31, 33, 36, on angiogenesis (*in vitro*)**

In order to determine the biological activity of the anti-FGFR4 monoclonal antibody 40-12 over the course of human endothelial cell angiogenesis, *in vitro* angiogenesis experiments were carried out using HUVEC cells stimulated with FGF2 in the presence of the antibody 40-12 or of the control antibody at increasing doses of 1 to 30 µg/ml (Figs. 8A and 8B).

In this context, the active anti-FGFR4 antagonist monoclonal antibody 40-12 is capable of inhibiting the FGF2-induced angiogenesis of HUVEC cells, at the dose of 30 µg/ml or 200 nM, whereas the control antibody 64-12 has no effect. Furthermore, the antibody 40-12 has no effect per se on the basal angiogenesis.

These results indicate that an FGF-R4-specific antagonist antibody is capable of inhibiting angiogenesis.

As for the antibody 40-12, the anti-FGFR4 antibodies of clones 8, 31, 33 and 36, derived from the phage display, were evaluated with regard to their ability to inhibit the FGF-2-induced angiogenesis of human endothelial cells of HUVEC type. These 4 antibodies block the *in vitro* stimulation of angiogenesis obtained with FGF-2, said antibodies being at the dose of 10 µg/ml (Figs. 8C and 8D).

Example 7: Antagonistic effect of the antibody 40-12 and of the antibodies derived from clones 8, 31, 33 and 36, on human hepatocarcinoma cells (*in vitro*)

In order to determine the antitumour effect of the anti-FGFR4 antagonist monoclonal antibody 40-12, experiments were carried out on Hep3b human hepatocarcinoma cells in which the proliferation and the signalling pathways resulting therein are dependent on the ligand-receptor pair: FGF19/FGF-R4.

Firstly, the study of the FGF-R4-dependent signalling pathways resulting in the proliferation of Hep3b cells was undertaken by Western blotting. This cell signalling involves the neosynthesis of the cFos and JunB proteins and also the phosphorylation of Erk1/2 (Lin and al., *J Biol Chem.*, 2007, 14:27277-84). To do this, 5×10^5 cells are seeded into dishes 35 mm in diameter, in 2 ml of complete medium (DMEM, 10% FCS, 2 mM glutamine). 24 h later, the cells are subjected to conditions of deficiency for 24 h in 1.8 ml of serum-free medium. The cells are then stimulated

for 3 h with 200 µl of 10-times concentrated FGF19, in the absence or in the presence of control anti-FGFR4 antibody or anti-FGFR4 antibody 40-12. The medium is then removed, and the cells are washed once with cold PBS and lysed on the dish for 30 min at 4°C with 75 µl of RIPA buffer supplemented with protease inhibitor. The total protein extract is then centrifuged for 10 min at 4°C at 13 000 rpm and the supernatant is analysed by the Western blotting technique. The membranes are then incubated for 2 h at ambient temperature in TBS, 0.05% tween, 5% milk and then the anti-cFos (Cell Signaling Technology, ref 2250), anti-JunB (Cell Signaling Technology, ref 3746) and anti-phosphoErk1/2 (Cell Signaling Technology, ref 4377) primary antibodies are added at 1/1000th and incubated overnight at 4°C with slow shaking. The membrane is rinsed three times with TBS, 0.05% tween, and the secondary antibody coupled to HRP is incubated for 4 h at 4°C, diluted to 1/2000th in TBS, 0.05% tween, 5% milk. The Western blotting results are then quantified using a Chemigenius machine (Syngene). The intensity of the bands obtained with the various antibodies are weighted with the intensity of the bands obtained with the anti-actin antibody directly coupled to HRP and used at 1/3000th (Santa Cruz Biotechnology, ref Sc-8432-HRP).

FGF19 at 30 ng/ml induces the synthesis of the JunB and cFos proteins and also the phosphorylation of Erk1/2 in Hep3b cells. This neosynthesis of protein and the phosphorylation of Erk are completely inhibited by the anti-FGFR4 antibody 40-12 at 100 µg/ml, whereas the control antibody has no inhibitory effect. These effects observed on the Western blotting membranes (Fig. 9A) are quantified and the intensities of the bands of each membrane are represented in the form of a graph (Fig. 9B).

Secondly, cell proliferation experiments per se were carried out. 5000 cells are seeded into a 96-well plate in 100 µl of DMEM medium, containing 10% FCS and 2 mM glutamine. 24 h later, the cells are serum deprived in a serum-free culture medium for 24 h. The Hep3b cells are then stimulated for 72 h with 100 µl of serum-free medium supplemented with 10 ng/ml of FGF19 (internal production at Sanofi-Aventis R&D) or with 10% of serum, in the absence or in the presence of control antibodies or of anti-FGFR4 antagonist monoclonal antibody 40-12. After 3 days, the cell proliferation is quantified using the CellTiter Glo kit (Promega, France).

It emerges from these experiments that serum and FGF19 are capable of stimulating Hep3b proliferation. The anti-FGFR4 antagonist antibody 40-12 partially inhibits this

serum-induced proliferation at 100 µg/ml, whereas the control antibody does not show any inhibitory activity (Fig. 10A). In addition, the antibody 40-12 at 10 µg/ml completely blocks the proliferation induced by FGF19 (Fig. 10B). The control antibody has no effect.

- 5 This demonstrates that the anti-FGFR4 antagonist antibody which is the subject of the invention can be used as an antitumour therapeutic agent in the context of FGF19-dependent or FGF-R4-dependent tumours, and that this antibody would be particularly effective in the treatment of hepatocarcinomas.

- 10 In order to simplify the study of the effect of the anti-FGFR4 antibodies on Hep3b cells, an ELISA assay was developed for detecting the phosphorylation of Erk1/2 following the stimulation of these cells with FGF-19 (in correlation with the experiments described in Example 8), FGF-2 or foetal calf serum.

- To do this, 50 000 Hep3b cells are seeded into 96-well black clear-bottom plates
15 (COSTAR, ref 3603) in 100 µl of DMEM medium containing 10% FCS and 2 mM glutamine. After 24 h, the cells are subjected to conditions of deficiency for 24 h in FCS-free DMEM medium containing 2 mM glutamine. The medium is then drawn off and replaced with 100 µl of deficiency medium preequilibrated at 37°C, containing FGF or FCS, and also the antibodies evaluated, at the various doses. The cells are
20 incubated for 3 h at 37°C, 5% CO₂. The stimulation medium is then drawn off, the wells are rinsed with PBS at 4°C and the cells are fixed by adding 200 µl of 4% PFA (paraformaldehyde) in PBS for 15 min at ambient temperature. The PFA is drawn off and the cells are washed three times with 200 µl of PBS. The antibody labelling for detecting phospho-Erk1/2 directly on the Hep3b cells begins by saturating the
25 nonspecific sites with 100 µl of saturation buffer (21.25 ml of PBS, 1.25 ml of 10% non-immune goat serum (Zymed, ref 50-062Z), 75 µl of triton X100) for 2 h. The saturation buffer is replaced with 50 µl of anti-phosphoErk1/2 primary antibody (Cell Signaling Technology, ref 4377) diluted to 1/100th in PBS buffer containing 1% BSA and 0.3% triton X100. The primary antibody is incubated with cells overnight at 4°C.
30 It is then rinsed off with 3 washes of 200 µl of PBS and revealed using an anti-rabbit secondary antibody coupled to AlexaFluor 488 (Molecular Probes, ref A11008) diluted to 1/5000th in PBS buffer containing 1% BSA and 0.3% triton X100 for 4 h. The secondary antibody is then rinsed off with 3 washes of 200 µl of PBS, and 100 µl of PBS is then added to each well. The fluorescence is read over with an EnVision

2103 Multilabel Reader (Perkin Elmer) using the FITC filter.

This technique makes it possible to confirm that FGF-19 at 30 ng/ml induces the phosphorylation of Erk1/2 in Hep3b cells and that 40-12 is capable of blocking this stimulation from doses of 3 µg/ml (Fig. 9C). FGF-2 and the serum are also capable
5 of inducing the system. In the latter 2 cases, the antibody 40-12 inhibits the effect of FGF-2 and of the serum at higher doses (30-100 µg/ml; Fig. 9C).

The detection of phospho-Erk1/2 by ELISA also made it possible to show that anti-FGFR4 antibodies that are active in the *in vitro* angiogenesis model are also capable of blocking between 70% and 95% of the phosphorylation of Erk1/2 induced
10 by FGF-19 at the dose of 3 µg/ml (Fig. 9D).

Advantageously, the antibodies of the present invention have an antagonistic effect both on the pathological angiogenesis associated with tumour development and on hepatic tumour growth per se, in particular on a model of hepatocarcinoma.

15

Example 8: Antagonistic effect of the antibody 40-12 in the murine model of pancreatic cancer

For this pharmacological model, female Rip1-Tag2 mice (Charles River Laboratory, France) with a C57Bl/6J genetic background are used. Starting from week 9 after birth, the animals have drinking water supplemented with 5% sucrose. The mice are treated from week 10 to week 12.5 in an intervention treatment protocol, once a week with a subcutaneous injection of the anti-FGFR4 antibody 40-12 or the control antibody, at the dose of 25 mg/kg (Fig. 14A). This protocol is approved by the
20 "Comité expérimentation Animale (Animal Care and Use Committee)" of Sanofi-Aventis Recherche. Our zootechnical facilities, the attention given to the animals and also the treatment protocols are in accordance with the principles laid down by the European Convention on the protection of vertebrate animals, sacrificed after the period of treatment or when the tumour burden and/or the side effects render their
25 withdrawal from the study obligatory.
30

For measuring the tumour burden, the animals are sacrificed by euthanasia at the end of the experiment and the tumours are microdissected from freshly excised pancreases. The tumour volume in mm³ is measured using a calliper rule, applying the formula [volume = 0.52 x (width)² x (length)] in order to approach the volume of a

spheroid. The tumour burden per mouse is calculated by the cumulation of the volume of the tumours of each mouse.

For the histochemical analysis of the vascular density, the animals are anaesthetized, and the pancreases are collected, fixed overnight in accustain® (Sigma) and then embedded in paraffin. Sections 5 µm thick are prepared for each sample. The endothelial cells are detected by incubating the sections with trypsin (Zymed, ref 00-3003) at 37°C for 10 min, and then with an anti-mouse CD31 antibody, produced in rats, diluted to 1/50th (BD Pharmingen). To reveal the regions labelled with the antibody, the sections are incubated with a biotin-coupled anti-rat antibody for 30 min, and then with HRP-coupled streptavidin, also for 30 min (Vectastain® ABC kit, Vector) and, finally, with DAB for 5 min (Vector, ref SK4100). The sections are then stained with hematoxylin diluted to 1/10th (Dako, S-3309). The photographs are taken with a camera mounted on a microscope (Nikon, E-800) at a total magnification of x200. The images are analysed using software (Visiolab, Biocom). The blood vessels in the tumour are counted and classified according to their surface area: small vessels between 5 and 20 µm², medium vessels between 21 and 100 µm² and large vessels starting from 101 µm². Two slides per pancreas are analysed in order to determine the vascular density corresponding to the total number of elements labelled per field.

20

In this model, the subcutaneous treatment using the anti-FGFR4 antibody 40-12 at 25 mg/kg once a week between the tenth and twelfth weeks makes it possible to significantly reduce the tumour burden by 55% (Fig11B) and has a tendency to reduce the number of tumours per pancreas by 34% (Fig. 11C), whereas the control treatment has no effect. This inhibition of tumour development by virtue of the anti-FGFR4 antibody 40-12 is accompanied by a significant reduction of 31% in the total vascular density (Fig. 11D) corresponding to an observed reduction in the number of blood vessels in all the vessel-size groups, labelled with an anti-CD31 antibody (Fig. 11D).

30

These *in vivo* results clearly show that an anti-FGFR4 antagonist antibody is capable of inhibiting the recruitment and the formation of blood vessels in the tumour. This inhibition of tumour vascularization is accompanied by a reduction in the number of tumours per pancreas and in the total tumour volume.

Advantageously, the antibodies of the present invention have an antagonistic effect both on pathological angiogenesis and on hepatic tumour growth (on a model of hepatocarcinoma) and pancreatic tumour growth.

5 Example 9: Cross-reactivity of the antibody with human, murine and rat FGF-R4s

Firstly, competition binding experiments were carried out. To do this, FGF2 was labelled on the 2 free cysteines with an AlexaFluor® 488 nm C-5 maleimide
10 (Molecular Probes, A10254) according to the supplier's recommendations. This FGF2-AF488, at 10 ng/ml, is capable of binding to the human FGF-R4s expressed at the surface of transfected 300-19 cells (Fig. 8). This binding is specific since the addition of excess unlabelled FGF2 makes it possible to displace the FGF2/FGF-R4 interaction (Fig. 8A). The same experiment was carried out with increasing doses of
15 the antibody 40-12 or of the control antibody 64-12 being added. Only the antagonist antibody 40-12 is capable of displacing the FGF2-AF488/FGF-R4 binding, with an IC_{50} of 3500 ng/ml, i.e. 23 nM, showing that the antagonistic effect of this antibody is due to its ability to displace FGF/FGF-R4 binding.

Secondly, and for the purpose of determining the ability of clone 40-12 to block
20 FGF/FGF-R4 binding in species other than humans, a dissociation experiment was carried out using the abovementioned mouse, rat and human FGF2/FGF-R4 pairs. To do this, murine FGF2 (R&D, ref 3139-FB-025) or rat FGF2 (R&D, ref 3339-FB-025) was labelled in the same way as human FGF2, with AlexaFluor 488. The dissociation experiments were carried out using the 300-19 lines transfected with
25 mouse or rat FGF-R4 receptors. The results show that the anti-FGFR4 antagonist antibody 40-12 is capable of dissociating the FGF2/FGF-R4 binding in a mouse or rat system, with the same effectiveness as in the human system. In fact, the IC_{50} values are 3500, 4110 and 3940 ng/ml, i.e. 23, 27 and 26 nM, for the human, murine or rat FGF2/FGF-R4 complexes, respectively (Fig. 13A, 13B and 13C, respectively).
30 This ability to bind to rodent FGF-R4 was verified by ELISA. The antibody 40-12 binds both to human FGF-R4 and to murine FGF-R4 (Fig. 12).

These results indicate that the anti-FGFR4 antibody 40-12 may be used in pharmacological models on rodents (at least mice and rats) and that the results obtained should be predictive of the effectiveness in humans.

Similarly, studies carried out on the antibodies derived from clones 8, 31, 33 and 36 show that these antibodies recognize both human FGF-R4 and murine FGF-R4 (Table 4 below)

5

Table 4: Kinetic parameters for binding of the anti-FGFR4 antibodies 8, 31, 33 and 36, measured by Surface Plasmon Resonance (BIAcore 3000):

	on h-FGFR4-Histag			on m-FGFR4-Histag		
	Kon ($M^{-1}s^{-1}$)	Koff (s^{-1})	KD (M)	Kon ($M^{-1}s^{-1}$)	Koff (s^{-1})	KD (M)
Clone 8	8.93×10^5	2.92×10^{-4}	3.27×10^{-10}	1.20×10^6	1.36×10^{-4}	1.15×10^{-10}
Clone 31	6.48×10^5	9.80×10^{-4}	1.52×10^{-9}	9.14×10^5	1.80×10^{-3}	1.97×10^{-9}
Clone 33	8.05×10^5	6.17×10^{-4}	7.71×10^{-10}	1.01×10^6	7.04×10^{-4}	6.92×10^{-10}
Clone 36	2.44×10^5	6.31×10^{-4}	2.62×10^{-9}	3.30×10^5	7.52×10^{-4}	2.28×10^{-9}

10

Example 10: Determination of the epitope recognized by the anti-FGF-R4 antibodies

A- Determination of the epitope recognized by the anti-FGFR4 antibody 40-12

15

A screen was carried out in order to determine the specific domain of FGFR4 recognized by the antibody 40-12, by ELISA assay. Through the use of a deleted form of the D1 domain of FGF-R4, in ELISA, it was established that the antibody 40-12 interacted with the D2-D3 domains of FGF-R4 (Fig. 12).

20

A second screen was carried out by ELISA assay, using, as capture antigen, the constructs containing either the D1 domain (SABVA4794) or the D2 domain (SABVA4796) or the D3 domain (SABVA4799) of the hFGFR4 protein, as described in Example 2. The capture antigen was bound to Immulon-4 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). The hybridoma 40-12 was subsequently added and then detection was carried out using the peroxidase-conjugated anti-mouse IgG rabbit antibody (Sigma; ref. A9044-dilution to 1:50 000). The revealing

25

was carried out with the TMB-H₂O₂ substrate (Interchim; ref UP664780) and the optical density (OD) measurements were carried out at 450 nm. Table 5 summarizes the results obtained:

- 5 Table 5: Measurement of the binding of the antibody 40-12 to the various subdomains of FGF-R4

Domain studied	D1 SABVA4794	D2 SABVA4796	D3 SABVA4799	D1-D3 FGFR4 -Fc
Signal (O.D., 450 nm)	0.185	3.000	0.105	3.000

- 10 The anti-FGFR4 antibody therefore recognizes the D2 domain of the extracellular portion of the FGFR4 protein.

Furthermore, the FGFR4-Fc protein denatured with FCS is not recognized by the antibody 40-12 in Western blotting analysis, thereby indicating that the epitope targeted by 40-12 on the D2 domain of FGFR4 is of conformational type.

- 15 B- Determination of the epitope recognized by the anti-FGFR4 antibodies 8, 31, 33, 36.

- 20 A screen was carried out in order to determine the specific domain of FGFR4 recognized by the antibodies 8, 31, 33 and 36, by ELISA assay using, as capture antigen, the constructs containing either the D2 and D3 domains (SEQ ID No. 42) or the hFGFR4-Histag protein (SABVA4614, SEQ ID No. 40). The capture antigen was bound to Immulon-4 enzyme-linked plates (VWR Scientific Inc. Swedesboro, NJ). Culture supernatants from HEK293 cells transiently transfected with plasmids which enable the secretion of the antibodies 8, 31, 33 and 36 were subsequently added
25 and then detection was carried out using the peroxidase-conjugated anti-human IgG rabbit antibody (DakoCytomation, ref. P0214-dilution to 1:5000). The revealing was carried out with the TMB-H₂O₂ substrate (Interchim; ref UP664780) and the optical density (OD) measurements were carried out at 450 nm. Table 6 below summarizes the results obtained:

30

Table 6: Binding of the antibodies derived from clones 8, 31, 33 and 36 to whole FGF-R4 or to the D2-D3 subdomain (OD signal at 450nm)

	hFGFR4-Histag	hFGFR4(D2,D3)-Histag
Clone 8	3.898	3.860
Clone 31	3.859	3.741
Clone 33	3.752	3.621
Clone 36	3.751	3.616

The antibodies 8, 31, 33 and 36 therefore recognize the D2-D3 domain of the extracellular portion of the FGFR4 protein.

5

Table 7: Sequences used, obtained and deduced

	Nucleotide sequences	Protein sequences
Antibody 40-12		
VH + CH	SEQ ID No. 1	SEQ ID No. 2
VL + CL	SEQ ID No. 3	SEQ ID No. 4
VH	SEQ ID No. 5	SEQ ID No. 6
VL	SEQ ID No. 7	SEQ ID No. 8
CDR VH		SEQ ID No. 9; 10; 11
CDR VL		SEQ ID No. 12; 13; 14
Antibody 64-12		
VH + CH	SEQ ID No. 15	SEQ ID No. 16
VL + CL	SEQ ID No. 17	SEQ ID No. 18
VH	SEQ ID No. 19	SEQ ID No. 20
VL	SEQ ID No. 21	SEQ ID No. 22
CDR VH		SEQ ID No. 23; 24; 25
CDR VL		SEQ ID No. 26; 27; 28

Humanized sequences		
Light chain 1	SEQ ID No. 29	SEQ ID No. 30
Light chain 2	SEQ ID No. 31	SEQ ID No. 32
Heavy chain 1	SEQ ID No. 33	SEQ ID No. 34
Heavy chain 2	SEQ ID No. 35	SEQ ID No. 36
Heavy chain 3	SEQ ID No. 37	SEQ ID No. 38
Constructs		
hFGFR4-Histag	SEQ ID No. 39	SEQ ID No. 40
hFGFR4-Streptag	SEQ ID No. 68	SEQ ID No. 69
hFGFR4(D2D3)-Histag	SEQ ID No. 41	SEQ ID No. 42
mFGFR4-Histag	SEQ ID No. 43	SEQ ID No. 44
hFGFR1-Fc	SEQ ID No. 45	SEQ ID No. 46
hFGFR2-Fc	SEQ ID No. 47	SEQ ID No. 48
rFGFR4	SEQ ID No. 49	SEQ ID No. 50
Primer sequences for establishing clonal line (Example 4)	SEQ ID No. 51; 52; 53; 54; 55; 56; 58 SEQ ID No. 61; 62	
FGFR4 transmembrane domain		SEQ ID No. 59; 60
Primer oligonucleotides Table 1	SEQ ID No. 63; 64; 65; 66; 67	
Epitope in D2 domain		SEQ ID No. 70

Antibody clone 8		
Whole light chain	SEQ ID No. 71	SEQ ID No. 72
Light chain CDR		SEQ ID No. 73; 74; 75
Whole heavy chain	SEQ ID No. 76	SEQ ID No. 77

Heavy chain CDR		SEQ ID No. 78; 79; 80
Antibody clone 31		
Whole light chain	SEQ ID No. 81	SEQ ID No. 82
Light chain CDR		SEQ ID No. 83; 84; 85
Whole heavy chain	SEQ ID No. 86	SEQ ID No. 87
Heavy chain CDR		SEQ ID No. 88; 89; 90
Antibody clone 33		
Whole light chain	SEQ ID No. 91	SEQ ID No. 92
Light chain CDR		SEQ ID No. 93; 94; 95
Whole heavy chain	SEQ ID No. 96	SEQ ID No. 97
Heavy chain CDR		SEQ ID No. 98; 99; 100
Antibody clone 36		
Whole light chain	SEQ ID No. 101	SEQ ID No. 102
Light chain CDR		SEQ ID No. 103; 104; 105
Whole heavy chain	SEQ ID No. 106	SEQ ID No. 107
Heavy chain CDR		SEQ ID No. 108; 109; 110
Subdomains of the extracellular portion of hFGFR4, fused to the Fc domain of IgG1		
fGFGR4_D1::Fc	SEQ ID No. 111	SEQ ID No. 112
fGFGR4_D2::Fc	SEQ ID No. 113	SEQ ID No. 114
fGFGR4_D3::Fc	SEQ ID No. 115	SEQ ID No. 116
Human IgG1 constant region sequence		SEQ ID No. 117

Claims

1. FGF-R4 receptor antagonist, characterized in that it is an antibody that specifically binds to FGF-R4.
2. Antagonist according to Claim 1, characterized in that it binds to the D2-D3 domain of the FGF-R4 receptor.
3. Antibody according to either of Claims 1 and 2, characterized in that it binds to the D2 domain of the FGF-R4 receptor.
4. Antagonist according to one of the preceding claims, characterized in that it has a K_D with respect to the FGF-R4 receptor, determined by the Surface Plasmon Resonance (Biacore) technique, of less than 10^{-8} M.
5. Antagonist according to one of the preceding claims, characterized in that it is active both against human FGF-R4 and against murine FGF-R4.
6. Antagonist according to one of the preceding claims, characterized in that it is an antibody and comprises at least one CDR having a sequence identical to one of the sequences SEQ ID No. 9, 10, 11, 12, 13, 14, 73, 74, 75, 78, 79, 80, 83, 84, 85, 88, 89, 90, 93, 94, 95, 98, 99, 100, 103, 104, 105, 108, 109 or 110.
7. Antagonist according to one of the preceding claims, characterized in that it is an antibody and comprises the CDRs of sequence SEQ ID Nos. 9, 10, 11, 12, 13 and 14; or 73, 74, 75, 78, 79 and 80; or 83, 84, 85, 88, 89 and 90; or 93, 94, 95, 98, 99 and 100; or 103, 104, 105, 108, 109 and 110, where one of the CDRs may differ by one or two amino acids compared with at least one of the sequences mentioned above, provided that the antibody keeps its binding specificity.
8. Antagonist according to one of the preceding claims, characterized in that it is an antibody of which the variable region of its heavy chain comprises a

nucleotide sequence having at least 80% identity with the sequence SEQ ID No. 5, 76, 86, 96 or 106.

- 5 9. Antagonist according to one of the preceding claims, characterized in that it is an antibody of which the variable region of its light chain comprises a nucleotide sequence having at least 80% identity with the sequence SEQ ID No. 7, 71, 81, 91 or 101.
- 10 10. Antagonist according to one of the preceding claims, characterized in that it is an antibody and in that its sequence comprises the polypeptide sequences SEQ ID Nos. 2 and 4; or 6 and 8; or 72 and 77; or 82 and 87; or 92 and 97; or 102 and 107.
- 15 11. Antagonist according to any one of the preceding claims, characterized in that it induces inhibition of the cell signalling pathways controlled by FGF-R4.
12. Antagonist according to any one of the preceding claims, characterized in that it induces inhibition of angiogenesis.
- 20 13. Antagonist according to any one of the preceding claims, characterized in that it induces inhibition of tumour cell proliferation.
- 25 14. Antagonist according to any one of the preceding claims, characterized in that its affinity for FGF-R4 is 10 times greater than its affinity for the other FGF receptors.
15. Antagonist according to any one of Claims 1 to 7, characterized in that it is a humanized antibody.
- 30 16. Antagonist according to any one of Claims 1 to 7, characterized in that it is a human antibody.
17. Antagonist according to Claim 15, characterized in that it comprises a variable light chain having at least 80% identity with one of the polypeptide sequences

SEQ ID No. 30 or 32.

- 5 18. Antagonist according to Claim 15, characterized in that it comprises a variable heavy chain having at least 80% identity with a sequence SEQ ID No. 34, 36 or 38.
19. Antagonist according to any one of the preceding claims, characterized in that it is an antibody and in that it is conjugated to a cytotoxic agent.
- 10 20. Use of an antagonist according to any one of the preceding claims, in the treatment of diseases associated with a pathological angiogenesis.
21. Use of an antagonist according to any one of the preceding claims, in the treatment of hepatocarcinomas or of any other type of hepatic cancer.
- 15 22. Use of an antagonist according to any one of the preceding claims, in the treatment of pancreatic cancer.
23. Pharmaceutical composition comprising an antagonist according to any one of Claims 1 to 19 and excipients.
- 20 24. Method of treating a disease related to a pathological angiogenesis, characterized in that it comprises the administration, to the patient, of an antibody according to any one of Claims 1 to 19.
- 25 25. Method of treating a cancer, characterized in that it comprises the administration, to the patient, of an antibody according to any one of Claims 1 to 19.
- 30 26. Cell line producing antibodies according to Claims 1 to 19.
27. Method of producing an antibody according to any one of Claims 1 to 19, characterized in that it comprises culturing a cell line according to Claim 26.

28. Drug comprising an antagonist according to any one of Claims 1 to 19.
29. Polynucleotide encoding a polypeptide having at least 80% identity with one of the sequences SEQ ID No. 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 30, 32, 34, 36, 38,
5 72, 73, 74, 75, 77, 78, 79, 80, 82, 83, 84, 85, 87, 88, 89, 90, 92, 93, 94, 95, 97, 98, 99, 100, 103, 104, 105, 107, 108, 109 or 110.
30. Polynucleotide characterized in that it has a sequence having at least 80% identity with one of the sequences SEQ ID No. 1, 3, 5, 7, 29, 31, 33, 35, or 37,
10 71, 76, 81, 86, 91, 96, 101 or 106.
31. Recombinant vector comprising a nucleic acid according to either one of Claims 29 and 30.
- 15 32. Host cell comprising a vector according to Claim 31.

pctfr2009051343-seq1
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atc Ile	ttc Phe	ccc Pro	cca Pro 260	aag Lys	ccc Pro	aag Lys	gat Asp	gtg Val 265	ctc Leu	acc Thr	att Ile	act Thr	ctg Leu 270	act Thr	cct Pro	816
aag Lys	gtc Val	acg Thr 275	tgt Cys	gtt Val	gtg Val	gta Val	gac Asp 280	atc Ile	agc Ser	aag Lys	gat Asp	gat Asp 285	ccc Pro	gag Glu	gtc Val	864
cag Gln 290	ttc Phe	agc Ser	tgg Trp	ttt Phe	gta Val	gat Asp 295	gat Asp	gtg Val	gag Glu	gtg Val	cac His 300	aca Thr	gct Ala	cag Gln	acg Thr	912
caa Gln 305	ccc Pro	cgg Arg	gag Glu	gag Glu	cag Gln 310	ttc Phe	aac Asn	agc Ser	act Thr	ttc Phe 315	cgc Arg	tca Ser	gtc Val	agt Ser	gaa Glu 320	960
ctt Leu	ccc Pro	atc Ile	atg Met	cac His 325	cag Gln	gac Asp	tgg Trp	ctc Leu	aat Asn 330	ggc Gly	aag Lys	gag Glu	ttc Phe	aaa Lys 335	tgc Cys	1008
agg Arg	gtc Val	aac Asn 340	agt Ser	gca Ala	gct Ala	ttc Phe	cct Pro	gcc Ala 345	ccc Pro	atc Ile	gag Glu	aaa Lys	acc Thr 350	atc Ile	tcc Ser	1056
aaa Lys	acc Thr	aaa Lys 355	ggc Gly	aga Arg	ccg Pro	aag Lys	gct Ala 360	cca Pro	cag Gln	gtg Val	tac Tyr	acc Thr 365	att Ile	cca Pro	cct Pro	1104
ccc Pro	aag Lys 370	gag Glu	cag Gln	atg Met	gcc Ala	aag Lys 375	gat Asp	aaa Lys	gtc Val	agt Ser	ctg Leu 380	acc Thr	tgc Cys	atg Met	ata Ile	1152
aca Thr 385	gac Asp	ttc Phe	ttc Phe	cct Pro	gaa Glu 390	gac Asp	att Ile	act Thr	gtg Val 395	gag Glu	tgg Trp	cag Gln	tgg Trp	aat Asn	ggg Gly 400	1200
cag Gln	cca Pro	gcg Ala	gag Glu	aac Asn 405	tac Tyr	aag Lys	aac Asn	act Thr	cag Gln 410	ccc Pro	atc Ile	atg Met	gac Asp 415	aca Thr	gat Asp	1248
ggc Gly	tct Ser	tac Tyr	ttc Phe 420	gtc Val	tac Tyr	agc Ser	aag Lys	ctc Leu 425	aat Asn	gtg Val	cag Gln	aag Lys	agc Ser 430	aac Asn	tgg Trp	1296
gag Glu	gca Ala	gga Gly 435	aat Asn	act Thr	ttc Phe	acc Thr	tgc Cys 440	tct Ser	gtg Val	tta Leu	cat His	gag Glu 445	ggc Gly	ctg Leu	cac His	1344
aac	cac	cat	act	gag	aag	agc	ctc	tcc	cac	tct	cct	ggt	aag	tga		1389

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Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
 450 455 460

<210> 2
 <211> 462
 <212> PRT
 <213> Mus sp.

<400> 2

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Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
 35 40 45

Ser Thr Ser Gly Met Gly Val Ser Trp Ile Arg Gln Pro Ser Gly Lys
 50 55 60

Gly Leu Glu Trp Leu Ala His Ile Tyr Trp Asp Asp Lys Arg Tyr
 65 70 75 80

Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser
 85 90 95

Asn Gln Val Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala
 100 105 110

Thr Tyr Tyr Cys Ala Arg Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr Trp
 115 120 125

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Lys Thr Thr Pro Pro
 130 135 140

Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met
 145 150 155 160

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
 165 170 175

Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
 180 185 190

Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
 195 200 205

Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His
 210 215 220

Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys
 Page 3

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225 230 235 240
 Gly Cys Lys Pro Cys₂₄₅ Ile Cys Thr Val Pro₂₅₀ Glu Val Ser Ser Val₂₅₅ Phe
 Ile Phe Pro Pro₂₆₀ Lys Pro Lys Asp Val₂₆₅ Leu Thr Ile Thr Leu Thr Pro
 Lys Val Thr₂₇₅ Cys Val Val Val Asp₂₈₀ Ile Ser Lys Asp Asp₂₈₅ Pro Glu Val
 Gln Phe Ser Trp Phe Val Asp₂₉₅ Asp Val Glu Val His₃₀₀ Thr Ala Gln Thr
 Gln Pro Arg Glu Glu Gln₃₁₀ Phe Asn Ser Thr Phe₃₁₅ Arg Ser Val Ser Glu₃₂₀
 Leu Pro Ile Met His₃₂₅ Gln Asp Trp Leu Asn₃₃₀ Gly Lys Glu Phe Lys₃₃₅ Cys
 Arg Val Asn Ser₃₄₀ Ala Ala Phe Pro Ala₃₄₅ Pro Ile Glu Lys Thr₃₅₀ Ile Ser
 Lys Thr Lys₃₅₅ Gly Arg Pro Lys Ala₃₆₀ Pro Gln Val Tyr Thr₃₆₅ Ile Pro Pro
 Pro Lys₃₇₀ Glu Gln Met Ala Lys₃₇₅ Asp Lys Val Ser Leu₃₈₀ Thr Cys Met Ile
 Thr Asp Phe Phe Pro Glu₃₉₀ Asp Ile Thr Val Glu₃₉₅ Trp Gln Trp Asn Gly₄₀₀
 Gln Pro Ala Glu Asn₄₀₅ Tyr Lys Asn Thr Gln₄₁₀ Pro Ile Met Asp Thr₄₁₅ Asp
 Gly Ser Tyr Phe Val Tyr Ser Lys Leu₄₂₅ Asn Val Gln Lys Ser₄₃₀ Asn Trp
 Glu Ala Gly₄₃₅ Asn Thr Phe Thr Cys₄₄₀ Ser Val Leu His Glu₄₄₅ Gly Leu His
 Asn His His Thr Glu Lys Ser₄₅₅ Leu Ser His Ser Pro₄₆₀ Gly Lys

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<220>
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 <222> (1)..(705)

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gcc tcc aga ggt gat att gtg cta act cag tct cca gcc acc ctg tct 96
 Ala Ser Arg Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
 20 25 30

gtg act cca gga gat aga gtc agt ctt tcc tgc agg gcc agt caa agt 144
 Val Thr Pro Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser
 35 40 45

att agc aac tac cta cac tgg tat caa caa aaa tca cat gag tct cca 192
 Ile Ser Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro
 50 55 60

agg ctt ctc atc aag tat gct tcc cag tcc atc tct ggg atc ccc tcc 240
 Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser
 65 70 75 80

agg ttc agt ggc agt gga tca ggg aca gat ttc att ctc agt ttc aac 288
 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Asn
 85 90 95

agt gtg gag act gaa gat ttt gga atg tat ttc tgt caa cag agt aac 336
 Ser Val Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn
 100 105 110

agc tgg cct ttc acg ttc ggc tcg ggg aca aaa ttg gaa ata aaa cgg 384
 Ser Trp Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
 115 120 125

gct gat gct gca cca act gta tcc atc ttc cca cca tcc agt gag cag 432
 Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
 130 135 140

tta aca tct gga ggt gcc tca gtc gtg tgc ttc ttg aac aac ttc tac 480
 Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
 145 150 155 160

ccc aaa gac atc aat gtc aag tgg aag att gat ggc agt gaa cga caa 528
 Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
 165 170 175

aat ggc gtc ctg aac agt tgg act gat cag gac agc aaa gac agc acc 576
 Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
 180 185 190

tac agc atg agc agc acc ctc acg ttg acc aag gac gag tat gaa cga 624
 Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
 195 200 205

cat aac agc tat acc tgt gag gcc act cac aag aca tca act tca ccc 672
 His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
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att gtc aag agc ttc aac agg aat gag tgt taa 705
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 225 230

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 <213> Mus sp.

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<400> 4

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Val Thr Pro Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45
Ile Ser Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro
50 55 60
Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Asn
85 90 95
Ser Val Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn
100 105 110
Ser Trp Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
115 120 125
Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
130 135 140
Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
145 150 155 160
Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
165 170 175
Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
180 185 190
Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
195 200 205
His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
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Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
225 230

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<220>

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<222> (29)..(442)

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 Leu Leu Leu Ile Val Pro Ala Tyr Val Leu Ser Gln Val Thr Leu Lys
 10 15 20

gag tct ggc cct ggg ata ttg cag ccc tcc cag acc ctc agt ctg act 148
 Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln Thr Leu Ser Leu Thr
 25 30 35 40

tgt tct ttc tct ggg ttt tca ctg agc act tct ggt atg ggt gtg agc 196
 Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser Gly Met Gly Val Ser
 45 50 55

tgg att cgt cag cct tca gga aag ggt ctg gag tgg ctg gca cac att 244
 Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu Trp Leu Ala His Ile
 60 65 70

tac tgg gat gat gac aag cgc tat aac cca tcc ctg aag agc cgg ctc 292
 Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser Leu Lys Ser Arg Leu
 75 80 85

aca atc tcc aag gat acc tcc agc aac cag gta ttc ctc aag atc acc 340
 Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val Phe Leu Lys Ile Thr
 90 95 100

agt gtg gac act gca gat act gcc aca tac tac tgt gct cga gat tac 388
 Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr Cys Ala Arg Asp Tyr
 105 110 115 120

tac gct agt agc ttt gac tac tgg ggc caa ggc acc act ctc aca gtc 436
 Tyr Ala Ser Ser Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
 125 130 135

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 Ser Ser

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<211> 138

<212> PRT

<213> Mus sp.

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Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln
 20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
 35 40 45

Ser Thr Ser Gly Met Gly Val Ser Trp Ile Arg Gln Pro Ser Gly Lys
 50 55 60

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Gly Leu Glu Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr
65 70 75 80

Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser
85 90 95

Asn Gln Val Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala
100 105 110

Thr Tyr Tyr Cys Ala Arg Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr Trp
115 120 125

Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
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<212> DNA
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<222> (18)..(401)

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Leu Phe Trp Ile Ser Ala Ser Arg Gly Asp Ile Val Leu Thr Gln Ser
15 20 25

cca gcc acc ctg tct gtg act cca gga gat aga gtc agt ctt tcc tgc 146
Pro Ala Thr Leu Ser Val Thr Pro Gly Asp Arg Val Ser Leu Ser Cys
30 35 40

agg gcc agt caa agt att agc aac tac cta cac tgg tat caa caa aaa 194
Arg Ala Ser Gln Ser Ile Ser Asn Tyr Leu His Trp Tyr Gln Gln Lys
45 50 55

tca cat gag tct cca agg ctt ctc atc aag tat gct tcc cag tcc atc 242
Ser His Glu Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile
60 65 70 75

tct ggg atc ccc tcc agg ttc agt ggc agt gga tca ggg aca gat ttc 290
Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
80 85 90

att ctc agt ttc aac agt gtg gag act gaa gat ttt gga atg tat ttc 338
Ile Leu Ser Phe Asn Ser Val Glu Thr Glu Asp Phe Gly Met Tyr Phe
95 100 105

tgt caa cag agt aac agc tgg cct ttc acg ttc ggc tcg ggg aca aaa 386
Cys Gln Gln Ser Asn Ser Trp Pro Phe Thr Phe Gly Ser Gly Thr Lys
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Leu Glu Ile Lys Arg
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Ala Ser Arg Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
 20 25 30

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

Ile Ser Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro
 50 55 60

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Asn
 85 90 95

Ser Val Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn
 100 105 110

Ser Trp Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg
 115 120 125

<210> 9
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Thr Ser Gly Met Gly Val Ser
 1 5

<210> 10
 <211> 16
 <212> PRT
 <213> Mus sp.

<400> 10

His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser Leu Lys Ser
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<400> 11

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Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr
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<210> 12
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<400> 12

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<210> 14
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Gln Gln Ser Asn Ser Trp Pro Phe Thr
1 5

<210> 15
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<212> DNA
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gtc	cag	tgt	gat	gtg	cag	ctg	gtg	gag	tct	ggg	gga	ggc	tta	gtg	cag	96
Val	Gln	Cys	Asp	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	
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cct	gga	ggg	tcc	cgg	aaa	ctc	tcc	tgt	gca	gcc	tct	gga	ttc	act	ttc	144
Pro	Gly	Gly	Ser	Arg	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	
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Ser	Asn	Phe	Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Glu	Lys	Gly	Leu	
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Glu	Trp	Val	Ala	Tyr	Ile	Ser	Ser	Gly	Ser	Ser	Thr	Ile	Tyr	Tyr	Ala	
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acc Thr	ctg Leu	ttc Phe	ctg Leu 100	caa Gln	atg Met	acc Thr	agt Ser	cta Leu 105	agg Arg	tct Ser	gag Glu	gac Asp	acg Thr 110	gcc Ala	atg Met	336
tat Tyr	tac Tyr	tgt Cys 115	gca Ala	aga Arg	tat Tyr	gat Asp	tac Tyr 120	gac Asp	gat Asp	gat Asp	tac Tyr	tat Tyr 125	gct Ala	atg Met	gaa Glu	384
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gcc Ala 225	cac His	ccg Pro	gcc Ala	agc Ser 230	agc Ser	acc Thr	aag Lys	gtg Val	gac Asp 235	aag Lys	aaa Lys	att Ile	gtg Val	ccc Pro	agg Arg 240	720
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gag Glu	gtc Val 290	cag Gln	ttc Phe	agc Ser	tgg Trp	ttt Phe 295	gta Val	gat Asp	gat Asp	gtg Val	gag Glu 300	gtg Val	cac His	aca Thr	gct Ala	912
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aaa Lys	tgc Cys	agg Arg	gtc Val 340	aac Asn	agt Ser	gca Ala	gct Ala	ttc Phe 345	cct Pro	gcc Ala	ccc Pro	atc Ile	gag Glu 350	aaa Lys	acc Thr	1056

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cca cct ccc aag gag cag atg gcc aag gat aaa gtc agt ctg acc tgc	1152
Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys	
370 375 380	
atg ata aca gac ttc ttc cct gaa gac att act gtg gag tgg cag tgg	1200
Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp	
385 390 395 400	
aat ggg cag cca gcg gag aac tac aag aac act cag ccc atc atg gac	1248
Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp	
405 410 415	
aca gat ggc tct tac ttc gtc tac agc aag ctc aat gtg cag aag agc	1296
Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser	
420 425 430	
aac tgg gag gca gga aat act ttc acc tgc tct gtg tta cat gag ggc	1344
Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly	
435 440 445	
ctg cac aac cac cat act gag aag agc ctc tcc cac tct cct ggt aag	1392
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tga	1395

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<400> 16

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Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
Ser Asn Phe Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu
50 55 60
Glu Trp Val Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala
65 70 75 80
Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn
85 90 95
Thr Leu Phe Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met
100 105 110
Tyr Tyr Cys Ala Arg Tyr Asp Tyr Asp Asp Tyr Tyr Ala Met Glu

pctfr2009051343-seq1
120 125

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr
130 135 140

Pro 145 Pro Ser Val Tyr Pro 150 Leu Ala Pro Gly Ser 155 Ala Ala Gln Thr Asn 160

Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro
165 170 175

Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr
180 185 190

Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val
195 200 205

Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val
210 215 220

Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg
225 230 235 240

Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser
245 250 255

Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu
260 265 270

Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro
275 280 285

Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala
290 295 300

Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val
305 310 315 320

Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe
325 330 335

Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr
340 345 350

Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile
355 360 365

Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys
370 375 380

Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp
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385 390 395 400

Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp
405 410 415

Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser
420 425 430

Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly
435 440 445

Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
450 455 460

<210> 17
<211> 705
<212> DNA
<213> Mus sp.

<220>
<221> CDS
<222> (1)..(705)

<400> 17
atg gcc tgg att tca ctt ata ctc tct ctc ctg gct ctc agc tca ggg 48
Met Ala Trp Ile Ser Leu Ile Leu Ser Leu Leu Ala Leu Ser Ser Gly
1 5 10 15
gcc att tcc cag gct gtt gtg act cag gaa tct gca ctc acc aca tca 96
Ala Ile Ser Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr Ser
20 25 30
cct ggt gaa aca gtc aca ctc act tgt cgc tca agt act ggg gct gtt 144
Pro Gly Glu Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val
35 40 45
aca act agt aac tat gcc aac tgg gtc caa gaa aaa cca gat cat tta 192
Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu
50 55 60
ttc act ggt cta ata ggt ggt acc aac aac cga gct cca ggt gtt cct 240
Phe Thr Gly Leu Ile Gly Gly Thr Asn Asn Arg Ala Pro Gly Val Pro
65 70 75 80
gcc aga ttc tca ggc tcc ctg att gga gac aag gct gcc ctc acc atc 288
Ala Arg Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile
85 90 95
aca ggg gca cag act gag gat gag gca ata tat ttc tgt gct cta tgg 336
Thr Gly Ala Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp
100 105 110
tac agc aac cat tgg gtg ttc ggt gga gga acc aaa ctg act gtc cta 384
Tyr Ser Asn His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
115 120 125
ggc cag ccc aag tct tcg cca tca gtc acc ctg ttt cca cct tcc tct 432
Gly Gln Pro Lys Ser Ser Pro Ser Val Thr Leu Phe 140
130 135 140
gaa gag ctc gag act aac aag gcc aca ctg gtg tgt acg atc act gat 480
Glu Glu Leu Glu Thr Asn Lys Ala Thr Leu Val Cys Thr Ile Thr Asp
145 150 155

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145		150		155		160	
ttc tac cca ggt gtg gtg aca gtg gac tgg aag gta gat ggt acc cct							528
Phe Tyr Pro Gly Val Val Thr Val Asp Trp Lys Val Asp Gly Thr Pro							
		165		170		175	
gtc act cag ggt atg gag aca acc cag cct tcc aaa cag agc aac aac							576
Val Thr Gln Gly Met Glu Thr Thr Gln Pro Ser Lys Gln Ser Asn Asn							
		180		185		190	
aag tac atg gct agc agc tac ctg acc ctg aca gca aga gca tgg gaa							624
Lys Tyr Met Ala Ser Ser Tyr Leu Thr Leu Thr Ala Arg Ala Trp Glu							
		195		200		205	
agg cat agc agt tac agc tgc cag gtc act cat gaa ggt cac act gtg							672
Arg His Ser Ser Tyr Ser Cys Gln Val Thr His Glu Gly His Thr Val							
		210		215		220	
gag aag agt ttg tcc cgt gct gac tgt tcc tag							705
Glu Lys Ser Leu Ser Arg Ala Asp Cys Ser							
		225		230			

<210> 18
 <211> 234
 <212> PRT
 <213> Mus sp.

<400> 18

Met Ala Trp Ile Ser Leu Ile Leu Ser Leu Leu Ala Leu Ser Ser Gly
1 5 10 15

Ala Ile Ser Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr Ser
20 25 30

Pro Gly Glu Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val
35 40 45

Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu
50 55 60

Phe Thr Gly Leu Ile Gly Gly Thr Asn Asn Arg Ala Pro Gly Val Pro
65 70 75 80

Ala Arg Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile
85 90 95

Thr Gly Ala Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp
100 105 110

Tyr Ser Asn His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
115 120 125

Gly Gln Pro Lys Ser Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
130 135 140

Glu Glu Leu Glu Thr Asn Lys Ala Thr Leu Val Cys Thr Ile Thr Asp
145 150 155 160

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Phe Tyr Pro Gly Val Val Thr Val Asp Trp Lys Val Asp Gly Thr Pro
165 170 175

Val Thr Gln Gly Met Glu Thr Thr Gln Pro Ser Lys Gln Ser Asn Asn
180 185 190

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

Arg His Ser Ser Tyr Ser Cys Gln Val Thr His Glu Gly His Thr Val
210 215 220

Glu Lys Ser Leu Ser Arg Ala Asp Cys Ser
225 230

<210> 19
<211> 420
<212> DNA
<213> Mus sp.

<220>
<221> CDS
<222> (1)..(420)

<400> 19
atg gac tcc agg ctc aat tta gtt ttc ctt gtc ctt att tta aaa ggt 48
Met Asp Ser Arg Leu Asn Leu Val Phe Leu Val Leu Ile Leu Lys Gly
1 5 10 15
gtc cag tgt gat gtg cag ctg gtg gag tct ggg gga ggc tta gtg cag 96
Val Gln Cys Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30
cct gga ggg tcc cgg aaa ctc tcc tgt gca gcc tct gga ttc act ttc 144
Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
agt aac ttt gga atg cac tgg gtt cgt cag gct cca gag aag gga ctg 192
Ser Asn Phe Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu
50 55 60
gag tgg gtc gca tac att agt agt ggc agt agt acc atc tac tat gca 240
Glu Trp Val Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala
65 70 75 80
gac aca gtg aag ggc cga ttc acc atc tcc aga gac aat ccc aag aac 288
Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn
85 90 95
acc ctg ttc ctg caa atg acc agt cta agg tct gag gac acg gcc atg 336
Thr Leu Phe Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met
100 105 110
tat tac tgt gca aga tat gat tac gac gat gat tac tat gct atg gaa 384
Tyr Tyr Cys Ala Arg Tyr Asp Tyr Asp Asp Asp Tyr Ala Met Glu
115 120 125
tac tgg ggt caa gga acc tca gtc acc gtc tcc tca 420
Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
130 135 140

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<210> 20
 <211> 140
 <212> PRT
 <213> Mus sp.

<400> 20

Met Asp Ser Arg Leu Asn Leu Val Phe Leu Val Leu Ile Leu Lys Gly
 1 5 10 15

Val Gln Cys Asp Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
 20 25 30

Pro Gly Gly Ser Arg Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45

Ser Asn Phe Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu
 50 55 60

Glu Trp Val Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala
 65 70 75 80

Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Pro Lys Asn
 85 90 95

Thr Leu Phe Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met
 100 105 110

Tyr Tyr Cys Ala Arg Tyr Asp Tyr Asp Asp Asp Tyr Tyr Ala Met Glu
 115 120 125

Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
 130 135 140

<210> 21
 <211> 412
 <212> DNA
 <213> Mus sp.

<220>
 <221> CDS
 <222> (29)..(412)

<400> 21
 tgaaaagaat agacctgggt tgtgaatt atg gcc tgg att tca ctt ata ctc 52
 Met Ala Trp Ile Ser Leu Ile Leu
 1 5

tct ctc ctg gct ctc agc tca ggg gcc att tcc cag gct gtt gtg act 100
 Ser Leu Leu Ala Leu Ser Ser Gly Ala Ile Ser Gln Ala Val Val Thr
 10 15 20

cag gaa tct gca ctc acc aca tca cct ggt gaa aca gtc aca ctc act 148
 Gln Glu Ser Ala Leu Thr Thr Ser Pro Gly Glu Thr Val Thr Leu Thr
 25 30 35 40

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tgt cgc tca agt act ggg gct gtt aca act agt aac tat gcc aac tgg 196
 Cys Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn Trp
 45 50 55
 gtc caa gaa aaa cca gat cat tta ttc act ggt cta ata ggt ggt acc 244
 Val Gln Glu Lys Pro Asp His Leu Phe Thr Gly Leu Ile Gly Gly Thr
 60 65 70
 aac aac cga gct cca ggt gtt cct gcc aga ttc tca ggc tcc ctg att 292
 Asn Asn Arg Ala Pro Gly Val Pro Ala Arg Phe Ser Gly Ser Leu Ile
 75 80 85
 gga gac aag gct gcc ctc acc atc aca ggg gca cag act gag gat gag 340
 Gly Asp Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln Thr Glu Asp Glu
 90 95 100
 gca ata tat ttc tgt gct cta tgg tac agc aac cat tgg gtg ttc ggt 388
 Ala Ile Tyr Phe Cys Ala Leu Trp Tyr Ser Asn His Trp Val Phe Gly
 105 110 115 120
 gga gga acc aaa ctg act gtc cta 412
 Gly Gly Thr Lys Leu Thr Val Leu
 125

<210> 22
 <211> 128
 <212> PRT
 <213> Mus sp.

<400> 22

Met Ala Trp Ile Ser Leu Ile Leu Ser Leu Leu Ala Leu Ser Ser Gly
 1 5 10 15
 Ala Ile Ser Gln Ala Val Val Thr Gln Glu Ser Ala Leu Thr Thr Ser
 20 25 30
 Pro Gly Glu Thr Val Thr Leu Thr Cys Arg Ser Ser Thr Gly Ala Val
 35 40 45
 Thr Thr Ser Asn Tyr Ala Asn Trp Val Gln Glu Lys Pro Asp His Leu
 50 55 60
 Phe Thr Gly Leu Ile Gly Gly Thr Asn Asn Arg Ala Pro Gly Val Pro
 65 70 75 80
 Ala Arg Phe Ser Gly Ser Leu Ile Gly Asp Lys Ala Ala Leu Thr Ile
 85 90 95
 Thr Gly Ala Gln Thr Glu Asp Glu Ala Ile Tyr Phe Cys Ala Leu Trp
 100 105 110
 Tyr Ser Asn His Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 115 120 125

<210> 23
 <211> 5
 <212> PRT
 <213> Mus sp.

<400> 23

Asn Phe Gly Met His
1 5

<210> 24

<211> 17

<212> PRT

<213> Mus sp.

<400> 24

Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val Lys
1 5 10 15

Gly

<210> 25

<211> 12

<212> PRT

<213> Mus sp.

<400> 25

Tyr Asp Tyr Asp Asp Asp Tyr Tyr Ala Met Glu Tyr
1 5 10

<210> 26

<211> 14

<212> PRT

<213> Mus sp.

<400> 26

Arg Ser Ser Thr Gly Ala Val Thr Thr Ser Asn Tyr Ala Asn
1 5 10

<210> 27

<211> 7

<212> PRT

<213> Mus sp.

<400> 27

Gly Thr Asn Asn Arg Ala Pro
1 5

<210> 28

<211> 9

<212> PRT

<213> Mus sp.

<400> 28

Ala Leu Trp Tyr Ser Asn His Trp Val
1 5

<210> 29

<211> 321

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<212> DNA
 <213> Artificial

<220>
 <223> Humanized sequence

<220>
 <221> CDS
 <222> (1)..(321)

<400> 29
 cag tct gcc ctg act cag tcc cca gca act ctc tct gtg tct ccc ggc 48
 Gln Ser Ala Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 caa tct gtg agc ctg tcc tgt cgg gca agc cag tct att tcc aat tat 96
 Gln Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
 20 25 30
 ctg cac tgg tat cag caa cac cca ggc gag agc cca cgg ctc ctg atc 144
 Leu His Trp Tyr Gln Gln His Pro Gly Glu Ser Pro Arg Leu Leu Ile
 35 40 45
 aaa tac gcc tct caa tcc att tct ggc tcc aac aga cgc ttc tct ggc 192
 Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ser Asn Arg Arg Phe Ser Gly
 50 55 60
 agc ggc tcc ggc acc gat ttc att ctc agc ttt aat agc gtt cag gca 240
 Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Asn Ser Val Gln Ala
 65 70 75 80
 gag gat ttt ggg atg tac ttc tgt caa cag agc aac tct tgg cct ttt 288
 Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Phe
 85 90 95
 acc ttc gga agc ggg act aaa ctg acc gtt ctg 321
 Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 30
 <211> 107
 <212> PRT
 <213> Artificial

<220>
 <223> synthetic Construct

<400> 30
 Gln Ser Ala Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 Gln Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
 20 25 30
 Leu His Trp Tyr Gln Gln His Pro Gly Glu Ser Pro Arg Leu Leu Ile
 35 40 45
 Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ser Asn Arg Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Asn Ser Val Gln Ala

65

70

75

80

Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp Pro Phe
 85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 31
 <211> 321
 <212> DNA
 <213> Artificial

<220>
 <223> Humanized sequence

<220>
 <221> CDS
 <222> (1)..(321)

<400> 31
 caa tct gca ctg act caa tct cca gca aca ctg tcc gtt tct cct gga 48
 Gln Ser Ala Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

caa tcc gtg agc ctc agc tgt agg gca tcc cag tcc att agc aac tat 96
 Gln Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
 20 25 30

ctc cac tgg tac cag cag cac cca gga gaa agc cct cgc ctg ctg ata 144
 Leu His Trp Tyr Gln Gln His Pro Gly Glu Ser Pro Arg Leu Leu Ile
 35 40 45

aaa tac gca agc cag tct att agc ggc agc aac cgg cgc ttc agc ggg 192
 Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ser Asn Arg Arg Phe Ser Gly
 50 55 60

tcc ggc tcc ggg aca gac ttt atc ctg tct ttt agc agc gtg caa gcc 240
 Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Ser Ser Val Gln Ala
 65 70 75 80

gaa gac ttt ggc atg tac ttc tgc cag cag tct aac aat tgg cca ttc 288
 Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Asn Trp Pro Phe
 85 90 95

acc ttc gga tcc ggc aca aag ctg acc gtg ctg 321
 Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Leu
 100 105

<210> 32
 <211> 107
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 32

Gln Ser Ala Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15

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Gln Ser Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
20 25 30

Leu His Trp Tyr Gln Gln His Pro Gly Glu Ser Pro Arg Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ser Asn Arg Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Ile Leu Ser Phe Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Asn Trp Pro Phe
85 90 95

Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Leu
100 105

<210> 33
<211> 342
<212> DNA
<213> Artificial

<220>
<223> Humanized sequence

<220>
<221> CDS
<222> (1)..(342)

<400> 33	
cag gtt act ctg aaa gaa tct ggc cca act ctg gtt aag cct aca cag	48
Gln Val Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln	
1 5 10 15	
acc ctg tcc ctc acc tgt tct ttc tcc ggc ttt agc ctg agc aca agc	96
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser	
20 25 30	
gga atg ggc gtc agc tgg atc aga caa cca ccc ggc aag ggc ctg gag	144
Gly Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu	
35 40 45	
tgg ctg gcc cac atc tat tgg gat gat gat aag agg tat aac cct tcc	192
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser	
50 55 60	
ctg aaa tcc aga ctc aca att tcc aag gac acc tcc agc aac cag gtc	240
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val	
65 70 75 80	
ttc ctg aag ata acc tct gtt gat cca gtg gac acc gca act tac tac	288
Phe Leu Lys Ile Thr Ser Val Asp Pro Val Asp Thr Ala Thr Tyr Tyr	
85 90 95	
tgc gcc cgc gac tac tat gcc agc tct ttt gac tac tgg ggg cag ggc	336
Cys Ala Arg Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr Trp Gly Gln Gly	
100 105 110	
aca ctc	342
Thr Leu	

pctfr2009051343-seq1

<210> 34
 <211> 114
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 34

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

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30

Gly Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
 35 40 45

Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
 65 70 75 80

Phe Leu Lys Ile Thr Ser Val Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95

Cys Ala Arg Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu

<210> 35
 <211> 342
 <212> DNA
 <213> Artificial

<220>
 <223> Humanized sequence

<220>
 <221> CDS
 <222> (1)..(342)

<400> 35

cag gtg act ctc aaa gaa tct ggc cct aca ctg gtg aaa ccc act cag 48
 Gln Val Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1 5 10 15

aca ctc agc ctg acc tgc tcc ttc agc ggc ttc tct ctg agc act tcc 96
 Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30

gga ctc gga gtg agc tgg att cgc caa cct cct ggg aaa ggc ctg gag 144
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Gly	Leu	Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu		
		35					40					45					
tgg	ctg	gca	cac	ata	tac	tgg	gat	gac	gac	aaa	cgc	tat	aac	cct	agc	192	
Trp	Leu	Ala	His	Ile	Tyr	Trp	Asp	Asp	Asp	Lys	Arg	Tyr	Asn	Pro	Ser		
	50					55					60						
ctg	aag	tcc	aga	ctc	aca	atc	tcc	aaa	gat	aca	tcc	agc	aat	cag	gtg	240	
Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Ser	Asn	Gln	Val		
65					70					75				80			
ttt	ctg	aag	atc	acc	tcc	gtc	gat	cca	gtc	gac	acc	gcc	act	tac	tat	288	
Phe	Leu	Lys	Ile	Thr	Ser	Val	Asp	Pro	Val	Asp	Thr	Ala	Thr	Tyr	Tyr		
				85					90					95			
tgt	gct	cgc	gat	tac	tat	gcc	agc	tcc	ttc	gac	tac	tgg	gga	cag	gga	336	
Cys	Ala	Arg	Asp	Tyr	Tyr	Ala	Ser	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly		
			100					105					110				
aca	ctg															342	
Thr	Leu																

<210> 36
 <211> 114
 <212> PRT
 <213> Artificial

<220>
 <223> Synthetic Construct

<400> 36

Gln	Val	Thr	Leu	Lys	Glu	Ser	Gly	Pro	Thr	Leu	Val	Lys	Pro	Thr	Gln		
1			5					10					15				
Thr	Leu	Ser	Leu	Thr	Cys	Ser	Phe	Ser	Gly	Phe	Ser	Leu	Ser	Thr	Ser		
			20				25					30					
Gly	Leu	Gly	Val	Ser	Trp	Ile	Arg	Gln	Pro	Pro	Gly	Lys	Gly	Leu	Glu		
		35					40					45					
Trp	Leu	Ala	His	Ile	Tyr	Trp	Asp	Asp	Asp	Lys	Arg	Tyr	Asn	Pro	Ser		
	50					55					60						
Leu	Lys	Ser	Arg	Leu	Thr	Ile	Ser	Lys	Asp	Thr	Ser	Ser	Asn	Gln	Val		
65					70				75					80			
Phe	Leu	Lys	Ile	Thr	Ser	Val	Asp	Pro	Val	Asp	Thr	Ala	Thr	Tyr	Tyr		
				85					90					95			
Cys	Ala	Arg	Asp	Tyr	Tyr	Ala	Ser	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly		
			100					105					110				
Thr	Leu																

<210> 37
 <211> 342

pctfr2009051343-seq1

<212> DNA
<213> Artificial

<220>
<223> Humanized sequence

<220>
<221> CDS
<222> (1)..(342)

<400> 37
cag gtc aca ctc aaa gaa tct gga cca aca ctc gtt aaa cca act caa 48
Gln Val Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15
aca ctc agc ctg act tgc agc ttt tct ggc ttc agc ctc tcc act agc 96
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
ggc ctc ggc gtg tcc tgg atc cgg cag ccc cct gga aaa ggc ctg gag 144
Gly Leu Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45
tgg ctg gcc cac atc tat tgg gac gat gac aag cgg tac aat cca agc 192
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60
ctg aaa tct cgg ctg acc ata tct aag gat act tct tcc aat cag gtg 240
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80
ttc ctg aag atc aca tct gtg gct cct gtc gac act gcc act tat tat 288
Phe Leu Lys Ile Thr Ser Val Ala Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95
tgc gca agg gat tac tac gca tcc tcc ttc gat tac tgg ggc cag gga 336
Cys Ala Arg Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr Trp Gly Gln Gly
100 105 110
act ctg 342
Thr Leu

<210> 38
<211> 114
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 38
Gln Val Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
Gly Leu Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
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50

55

60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Gln Val
65 70 75 80

Phe Leu Lys Ile Thr Ser Val Ala Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Asp Tyr Tyr Ala Ser Ser Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu

<210> 39
<211> 1059
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1059)

<400> 39
ctg gag gcc tct gag gaa gtg gag ctt gag ccc tgc ctg gct ccc agc 48
Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro Cys Leu Ala Pro Ser
1 5 10 15
ctg gag cag caa gag cag gag ctg aca gta gcc ctt ggg cag cct gtg 96
Leu Glu Gln Gln Glu Gln Glu Leu Thr Val Ala Leu Gly Gln Pro Val
20 25 30
cgg ctg tgc tgt ggg cgg gct gag cgt ggt ggc cac tgg tac aag gag 144
Arg Leu Cys Cys Gly Arg Ala Glu Arg Gly Gly His Trp Tyr Lys Glu
35 40 45
ggc agt cgc ctg gca cct gct ggc cgt gta cgg ggc tgg agg ggc cgc 192
Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg Gly Trp Arg Gly Arg
50 55 60
cta gag att gcc agc ttc cta cct gag gat gct ggc cgc tac ctc tgc 240
Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala Gly Arg Tyr Leu Cys
65 70 75 80
ctg gca cga ggc tcc atg atc gtc ctg cag aat ctc acc ttg att aca 288
Leu Ala Arg Gly Ser Met Ile Val Leu Gln Asn Leu Thr Leu Ile Thr
85 90 95
ggt gac tcc ttg acc tcc agc aac gat gat gag gac ccc aag tcc cat 336
Gly Asp Ser Leu Thr Ser Ser Asn Asp Asp Glu Asp Pro Lys Ser His
100 105 110
agg gac ctc tcg aat agg cac agt tac ccc cag caa gca ccc tac tgg 384
Arg Asp Leu Ser Asn Arg His Ser Tyr Pro Gln Gln Ala Pro Tyr Trp
115 120 125
aca cac ccc cag cgc atg gag aag aaa ctg cat gca gta cct gcg ggg 432
Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala Val Pro Ala Gly
130 135 140
aac acc gtc aag ttc cgc tgt cca gct gca ggc aac ccc acg ccc acc 480
Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly Asn Pro Thr Pro Thr

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145	150	155	160	
atc cgc tgg ctt aag gat gga cag gcc ttt cat ggg gag aac cgc att				528
Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg Ile				
	165	170	175	
gga ggc att cgg ctg cgc cat cag cac tgg agt ctc gtg atg gag agc				576
Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu Val Met Glu Ser				
	180	185	190	
gtg gtg ccc tcg gac cgc ggc aca tac acc tgc ctg gta gag aac gct				624
Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn Ala				
	195	200	205	
gtg ggc agc atc cgt tat aac tac ctg cta gat gtg ctg gag cgg tcc				672
Val Gly Ser Ile Arg Tyr Asn Tyr Leu Leu Asp Val Leu Glu Arg Ser				
	210	215	220	
ccg cac cgg ccc atc ctg cag gcc ggg ctc ccg gcc aac acc aca gcc				720
Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr Ala				
	225	230	235	240
gtg gtg ggc agc gac gtg gag ctg ctg tgc aag gtg tac agc gat gcc				768
Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp Ala				
	245	250	255	
cag ccc cac atc cag tgg ctg aag cac atc gtc atc aac ggc agc agc				816
Gln Pro His Ile Gln Trp Leu Lys His Ile Val Ile Asn Gly Ser Ser				
	260	265	270	
ttc gga gcc gac ggt ttc ccc tat gtg caa gtc cta aag act gca gac				864
Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu Lys Thr Ala Asp				
	275	280	285	
atc aat agc tca gag gtg gag gtc ctg tac ctg cgg aac gtg tca gcc				912
Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu Arg Asn Val Ser Ala				
	290	295	300	
gag gac gca ggc gag tac acc tgc ctc gca ggc aat tcc atc ggc ctc				960
Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu				
	305	310	315	320
tcc tac cag tct gcc tgg ctc acg gtg ctg cca gag gag gac ccc aca				1008
Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu Glu Asp Pro Thr				
	325	330	335	
tgg acc gca gca gcg ccc gag gcc gct agc cat cac cat cat cat cac				1056
Trp Thr Ala Ala Ala Pro Glu Ala Ala Ser His His His His His His				
	340	345	350	
tga				1059

<210> 40
 <211> 352
 <212> PRT
 <213> Homo sapiens

<400> 40

Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro Cys Leu Ala Pro Ser
1 5 10 15

Leu Glu Gln Gln Glu Gln Glu Leu Thr Val Ala Leu Gly Gln Pro Val
20 25 30

Arg Leu Cys Cys Gly Arg Ala Glu Arg Gly Gly His Trp Tyr Lys Glu
 35 40 45
 Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg Gly Trp Arg Gly Arg
 50 55 60
 Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala Gly Arg Tyr Leu Cys
 65 70 75 80
 Leu Ala Arg Gly Ser Met Ile Val Leu Gln Asn Leu Thr Leu Ile Thr
 85 90 95
 Gly Asp Ser Leu Thr Ser Ser Asn Asp Asp Glu Asp Pro Lys Ser His
 100 105 110
 Arg Asp Leu Ser Asn Arg His Ser Tyr Pro Gln Gln Ala Pro Tyr Trp
 115 120 125
 Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala Val Pro Ala Gly
 130 135 140
 Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly Asn Pro Thr Pro Thr
 145 150 155 160
 Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg Ile
 165 170 175
 Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu Val Met Glu Ser
 180 185 190
 Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn Ala
 195 200 205
 Val Gly Ser Ile Arg Tyr Asn Tyr Leu Leu Asp Val Leu Glu Arg Ser
 210 215 220
 Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr Ala
 225 230 235 240
 Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp Ala
 245 250 255
 Gln Pro His Ile Gln Trp Leu Lys His Ile Val Ile Asn Gly Ser Ser
 260 265 270
 Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu Lys Thr Ala Asp
 275 280 285
 Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu Arg Asn Val Ser Ala
 290 295 300

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Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu
305 310 315 320

Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu Glu Asp Pro Thr
325 330 335

Trp Thr Ala Ala Ala Pro Glu Ala Ala Ser His His His His His His
340 345 350

<210> 41
<211> 726
<212> DNA
<213> Homo sapiens

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

<400> 41
ctg gag gcc tct gag gaa gtg gag ctt gag ccc tgc caa gca ccc tac 48
Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro Cys Gln Ala Pro Tyr
1 5 10 15
tgg aca cac ccc cag cgc atg gag aag aaa ctg cat gca gta cct gcg 96
Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala Val Pro Ala
20 25 30
ggg aac acc gtc aag ttc cgc tgt cca gct gca ggc aac ccc acg ccc 144
Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly Asn Pro Thr Pro
35 40 45
acc atc cgc tgg ctt aag gat gga cag gcc ttt cat ggg gag aac cgc 192
Thr Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg
50 55 60
att gga ggc att cgg ctg cgc cat cag cac tgg agt ctc gtg atg gag 240
Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu Val Met Glu
65 70 75 80
agc gtg gtg ccc tcg gac cgc ggc aca tac acc tgc ctg gta gag aac 288
Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn
85 90 95
gct gtg ggc agc atc cgt tat aac tac ctg cta gat gtg ctg gag cgg 336
Ala Val Gly Ser Ile Arg Tyr Asn Tyr Leu Leu Asp Val Leu Glu Arg
100 105 110
tcc ccg cac cgg ccc atc ctg cag gcc ggg ctc ccg gcc aac acc aca 384
Ser Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr
115 120 125
gcc gtg gtg ggc agc gac gtg gag ctg ctg tgc aag gtg tac agc gat 432
Ala Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp
130 135 140
gcc cag ccc cac atc cag tgg ctg aag cac atc gtc atc aac ggc agc 480
Ala Gln Pro His Ile Gln Trp Leu Lys His Ile Val Ile Asn Gly Ser
145 150 155 160
agc ttc gga gcc gac ggt ttc ccc tat gtg caa gtc cta aag act gca 528
Ser Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu Lys Thr Ala
165 170 175
gac atc aat agc tca gag gtg gag gtc ctg tac ctg cgg aac gtg tca 576

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Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu	Arg	Asn	Val	Ser		
		180						185					190				
gcc	gag	gac	gca	ggc	gag	tac	acc	tgc	ctc	gca	ggc	aat	tcc	atc	ggc		624
Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	Gly		
		195					200					205					
ctc	tcc	tac	cag	tct	gcc	tgg	ctc	acg	gtg	ctg	cca	gag	gag	gac	ccc		672
Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro	Glu	Glu	Asp	Pro		
	210					215					220						
aca	tgg	acc	gca	gca	gcg	ccc	gag	gcc	gct	agc	cat	cac	cat	cat	cat		720
Thr	Trp	Thr	Ala	Ala	Ala	Pro	Glu	Ala	Ala	Ser	His	His	His	His	His		
	225				230					235					240		
cac	tga																726
His																	

<210> 42
 <211> 241
 <212> PRT
 <213> Homo sapiens

<400> 42

Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro	Cys	Gln	Ala	Pro	Tyr		
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Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala		
			20					25					30				
Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly	Asn	Pro	Thr	Pro		
	35						40					45					
Thr	Ile	Arg	Trp	Leu	Lys	Asp	Gly	Gln	Ala	Phe	His	Gly	Glu	Asn	Arg		
	50					55					60						
Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser	Leu	Val	Met	Glu		
	65				70					75					80		
Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys	Leu	Val	Glu	Asn		
				85					90					95			
Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp	Val	Leu	Glu	Arg		
			100					105					110				
Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Thr	Thr		
		115					120					125					
Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys	Val	Tyr	Ser	Asp		
	130					135					140						
Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val	Ile	Asn	Gly	Ser		
	145				150					155					160		
Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val	Leu	Lys	Thr	Ala		

Asp Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu Arg Asn Val Ser
180 185 190

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

Leu Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu Glu Asp Pro
210 215 220

Thr Trp Thr Ala Ala Ala Pro Glu Ala Ala Ser His His His His His
225 230 235 240

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<210> 43
<211> 1059
<212> DNA
<213> Mus sp.

<220>
<221> CDS
<222> (1)..(1059)

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ctg gag cag caa gag cag gtg ttg acg gtg gcc ctg ggg cag cct gtg	96
Leu Glu Gln Gln Glu Gln Val Leu Thr Val Ala Leu Gly Gln Pro Val	
20 25 30	
agg ctg tgc tgt ggg cgc acc gag cgt ggt cgt cac tgg tac aaa gag	144
Arg Leu Cys Cys Gly Arg Thr Glu Arg Gly Arg His Trp Tyr Lys Glu	
35 40 45	
ggc agc cgc cta gca tct gct ggg cga gta cgg ggt tgg aga ggc cgc	192
Gly Ser Arg Leu Ala Ser Ala Gly Arg Val Arg Gly Trp Arg Gly Arg	
50 55 60	
ctg gag atc gcc agc ttc ctt cct gag gat gct ggc cga tac ctc tgc	240
Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala Gly Arg Tyr Leu Cys	
65 70 75 80	
ctg gcc cgt ggc tcc atg acc gtc gta cac aat ctt acg ttg ctt atg	288
Leu Ala Arg Gly Ser Met Thr Val Val His Asn Leu Thr Leu Met	
85 90 95	
gat gac tcc tta acc tcc atc agt aat gat gaa gac ccc aag aca ctc	336
Asp Asp Ser Leu Thr Ser Ile Ser Asn Asp Glu Asp Pro Lys Thr Leu	
100 105 110	
agc agc tcc tcg agt ggt cat gtc tac cca cag caa gca ccc tac tgg	384
Ser Ser Ser Ser Ser Gly His Val Tyr Pro Gln Gln Ala Pro Tyr Trp	
115 120 125	
aca cac ccc caa cgc atg gag aag aaa ctg cat gca gtg cct gcc ggg	432
Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala Val Pro Ala Gly	

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130	135	140	
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atc cac tgg ctc aag gat gga cag gcc ttc cac ggg gag aat cgt att Ile His Trp Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg Ile 165 170 175			528
gga ggc att cgg ctg cgc cac caa cac tgg agc ctg gtg atg gaa agt Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu Val Met Glu Ser 180 185 190			576
gtg gta ccc tcg gac cgt ggc aca tac aca tgc ctt gtg gag aac tct Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn Ser 195 200 205			624
ctg ggt agc att cgc tac agc tat ctc ctg gat gtg ctg gag cgg tcc Leu Gly Ser Ile Arg Tyr Ser Tyr Leu Leu Asp Val Leu Glu Arg Ser 210 215 220			672
ccg cac cgg ccc atc ctg cag gcg ggg ctc cca gcc aac acc aca gct Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr Ala 225 230 235 240			720
gtg gtg ggc agc gac gtg gag cta ctc tgc aag gtg tac agc gac gcc Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp Ala 245 250 255			768
cag ccc cac ata cag tgg ctg aaa cac gtc gtc atc aac ggc agc agc Gln Pro His Ile Gln Trp Leu Lys His Val Val Ile Asn Gly Ser Ser 260 265 270			816
ttc ggc gcc gac ggt ttc ccc tac gta caa gtc ctg aag aca aca gac Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu Lys Thr Thr Asp 275 280 285			864
atc aat agc tcg gag gta gag gtc ttg tat ctg agg aac gtg tcc gct Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu Arg Asn Val Ser Ala 290 295 300			912
gag gat gca gga gag tat acc tgt ctg gcg ggc aac tcc atc ggc ctt Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu 305 310 315 320			960
tcc tac cag tca gcg tgg ctc acg gtg ctg cca gag gaa gac ctc acg Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu Glu Asp Leu Thr 325 330 335			1008
tgg aca aca gca acc cct gag gcc gct agc cat cac cat cat cat cac Trp Thr Thr Ala Thr Pro Glu Ala Ala Ser His His His His His His 340 345 350			1056
tga			1059
<210> 44			
<211> 352			
<212> PRT			
<213> Mus sp.			
<400> 44			
Leu Glu Ala Ser Glu Glu Met Glu Gln Glu Pro Cys Leu Ala Pro Ile 1 5 10 15			

Leu Glu Gln Gln Glu Gln Val Leu Thr Val Ala Leu Gly Gln Pro Val
 20 25 30
 Arg Leu Cys Cys Gly Arg Thr Glu Arg Gly Arg His Trp Tyr Lys Glu
 35 40 45
 Gly Ser Arg Leu Ala Ser Ala Gly Arg Val Arg Gly Trp Arg Gly Arg
 50 55 60
 Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala Gly Arg Tyr Leu Cys
 65 70 75 80
 Leu Ala Arg Gly Ser Met Thr Val Val His Asn Leu Thr Leu Leu Met
 85 90 95
 Asp Asp Ser Leu Thr Ser Ile Ser Asn Asp Glu Asp Pro Lys Thr Leu
 100 105 110
 Ser Ser Ser Ser Ser Gly His Val Tyr Pro Gln Gln Ala Pro Tyr Trp
 115 120 125
 Thr His Pro Gln Arg Met Glu Lys Lys Leu His Ala Val Pro Ala Gly
 130 135 140
 Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly Asn Pro Met Pro Thr
 145 150 155 160
 Ile His Trp Leu Lys Asp Gly Gln Ala Phe His Gly Glu Asn Arg Ile
 165 170 175
 Gly Gly Ile Arg Leu Arg His Gln His Trp Ser Leu Val Met Glu Ser
 180 185 190
 Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys Leu Val Glu Asn Ser
 195 200 205
 Leu Gly Ser Ile Arg Tyr Ser Tyr Leu Leu Asp Val Leu Glu Arg Ser
 210 215 220
 Pro His Arg Pro Ile Leu Gln Ala Gly Leu Pro Ala Asn Thr Thr Ala
 225 230 235 240
 Val Val Gly Ser Asp Val Glu Leu Leu Cys Lys Val Tyr Ser Asp Ala
 245 250 255
 Gln Pro His Ile Gln Trp Leu Lys His Val Val Ile Asn Gly Ser Ser
 260 265 270
 Phe Gly Ala Asp Gly Phe Pro Tyr Val Gln Val Leu Lys Thr Thr Asp
 275 280 285

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Ile Asn Ser Ser Glu Val Glu Val Leu Tyr Leu Arg Asn Val Ser Ala
 290 295 300

Glu Asp Ala Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly Leu
 305 310 315 320

Ser Tyr Gln Ser Ala Trp Leu Thr Val Leu Pro Glu Glu Asp Leu Thr
 325 330 335

Trp Thr Thr Ala Thr Pro Glu Ala Ala Ser His His His His His His
 340 345 350

<210> 45
 <211> 1773
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(1773)

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gtg gaa gtg gag tcc ttc ctg gtc cac ccc ggt gac ctg ctg cag ctt	96
Val Glu Val Glu Ser Phe Leu Val His Pro Gly Asp Leu Leu Gln Leu	
20 25 30	
cgc tgt cgg ctg cgg gac gat gtg cag agc atc aac tgg ctg cgg gac	144
Arg Cys Arg Leu Arg Asp Asp Val Gln Ser Ile Asn Trp Leu Arg Asp	
35 40 45	
ggg gtg cag ctg gcg gaa agc aac cgc acc cgc atc aca ggg gag gag	192
Gly Val Gln Leu Ala Glu Ser Asn Arg Thr Arg Ile Thr Gly Glu Glu	
50 55 60	
gtg gag gtg cag gac tcc gtg ccc gca gac tcc ggc ctc tat gct tgc	240
Val Glu Val Gln Asp Ser Val Pro Ala Asp Ser Gly Leu Tyr Ala Cys	
65 70 75 80	
gta acc agc agc ccc tcg ggc agt gac acc acc tac ttc tcc gtc aat	288
Val Thr Ser Ser Pro Ser Gly Ser Asp Thr Thr Tyr Phe Ser Val Asn	
85 90 95	
gtt tca gat gct ctc ccc tcc tcg gag gat gat gat gat gat gat gac	336
Val Ser Asp Ala Leu Pro Ser Ser Glu Asp Asp Asp Asp Asp Asp Asp	
100 105 110	
tcc tct tca gag gag aaa gaa aca gat aac acc aaa cca aac cgt atg	384
Ser Ser Ser Glu Glu Lys Glu Thr Asp Asn Thr Lys Pro Asn Arg Met	
115 120 125	
ccc gta gct cca tat tgg aca tcc cca gaa aag atg gaa aag aaa ttg	432
Pro Val Ala Pro Tyr Trp Thr Ser Pro Glu Lys Met Glu Lys Lys Leu	
130 135 140	
cat gca gtg ccg gct gcc aag aca gtg aag ttc aaa tgc cct tcc agt	480
His Ala Val Pro Ala Ala Lys Thr Val Lys Phe Lys Cys Pro Ser Ser	
145 150 155 160	
ggg acc cca aac ccc aca ctg cgc tgg ttg aaa aat ggc aaa gaa ttc	528

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Gly	Thr	Pro	Asn	Pro 165	Thr	Leu	Arg	Trp	Leu 170	Lys	Asn	Gly	Lys	Glu 175	Phe	
aaa Lys	cct Pro	gac Asp	cac His 180	aga Arg	att Ile	gga Gly	ggc Gly	tac Tyr 185	aag Lys	gtc Val	cgt Arg	tat Tyr	gcc Ala 190	acc Thr	tgg Trp	576
agc Ser	atc Ile	ata Ile 195	atg Met	gac Asp	tct Ser	gtg Val	gtg Val 200	ccc Pro	tct Ser	gac Asp	aag Lys	ggc Gly 205	aac Asn	tac Tyr	acc Thr	624
tgc Cys	att Ile 210	gtg Val	gag Glu	aat Asn	gag Glu	tac Tyr 215	ggc Gly	agc Ser	atc Ile	aac Asn	cac His 220	aca Thr	tac Tyr	cag Gln	ctg Leu	672
gat Asp 225	gtc Val	gtg Val	gag Glu	cgg Arg	tcc Ser 230	cct Pro	cac His	cgg Arg	ccc Pro	atc Ile 235	ctg Leu	caa Gln	gca Ala	ggg Gly	ttg Leu 240	720
ccc Pro	gcc Ala	aac Asn	aaa Lys	aca Thr 245	gtg Val	gcc Ala	ctg Leu	ggt Gly	agc Ser 250	aac Asn	gtg Val	gag Glu	ttc Phe	atg Met 255	tgt Cys	768
aag Lys	gtg Val	tac Tyr	agt Ser 260	gac Asp	ccg Pro	cag Gln	ccg Pro	cac His 265	atc Ile	cag Gln	tgg Trp	cta Leu	aag Lys 270	cac His	atc Ile	816
gag Glu	gtg Val	aat Asn 275	ggg Gly	agc Ser	aag Lys	att Ile	ggc Gly 280	cca Pro	gac Asp	aac Asn	ctg Leu	cct Pro 285	tat Tyr	gtc Val	cag Gln	864
atc Ile 290	ttg Leu	aag Lys	act Thr	gct Ala	gga Gly	gtt Val 295	aat Asn	acc Thr	acc Thr	gac Asp	aaa Lys 300	gag Glu	atg Met	gag Glu	gtg Val	912
ctt Leu 305	cac His	tta Leu	aga Arg	aat Asn	gtc Val 310	tcc Ser	ttt Phe	gag Glu	gac Asp	gca Ala 315	ggg Gly	gag Glu	tat Tyr	acg Thr	tgc Cys 320	960
ttg Leu	gcg Ala	ggt Gly	aac Asn	tct Ser 325	atc Ile	gga Gly	ctc Leu	tcc Ser	cat His 330	cac His	tct Ser	gca Ala	tgg Trp	ttg Leu 335	acc Thr	1008
gtt Val	ctg Leu	gaa Glu	gcc Ala 340	ctg Leu	gaa Glu	gag Glu	agg Arg	ccg Pro 345	gca Ala	gtg Val	atg Met	acc Thr	tcg Ser 350	ccc Pro	ctg Leu	1056
tac Tyr	ctg Leu	gag Glu 355	ata Ile	gcg Ala	cta Leu	gag Glu	ccc Pro 360	aaa Lys	tct Ser	tgt Cys	gac Asp	aaa Lys 365	act Thr	cac His	aca Thr	1104
tgc Cys	cca Pro 370	ccg Pro	tgc Cys	cca Pro	gca Ala	cct Pro 375	gaa Glu	ctc Leu	ctg Leu	ggg Gly	gga Gly 380	ccg Pro	tca Ser	gtc Val	ttc Phe	1152
ctc Leu 385	ttc Phe	ccc Pro	cca Pro	aaa Lys	ccc Pro 390	aag Lys	gac Asp	acc Thr	ctc Leu	atg Met 395	atc Ile	tcc Ser	cgg Arg	acc Thr	cct Pro 400	1200
gag Glu	gtc Val	aca Thr	tgc Cys	gtg Val 405	gtg Val	gtg Val	gac Asp	gtg Val	agc Ser 410	cac His	gaa Glu	gac Asp	cct Pro	gag Glu 415	gtc Val	1248
aag Lys	ttc Phe	aac Asn	tgg Trp 420	tac Tyr	gtg Val	gac Asp	ggc Gly	gtg Val 425	gag Glu	gtg Val	cat His	aat Asn	gcc Ala 430	aag Lys	aca Thr	1296
aag	ccg	cgg	gag	gag	cag	tac	aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	1344

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Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
		435					440					445				
ctc	acc	gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	aag	gag	tac	aag	tgc	1392
Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
		450				455					460					
aag	gtc	tcc	aac	aaa	gcc	ctc	cca	gcc	ccc	atc	gag	aaa	acc	atc	tcc	1440
Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	
		465			470					475					480	
aaa	gcc	aaa	ggg	cag	ccc	cga	gaa	cca	cag	gtg	tac	acc	ctg	ccc	cca	1488
Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
				485					490					495		
tcc	cgg	gat	gag	ctg	acc	aag	aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	1536
Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
			500					505					510			
aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	1584
Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
		515					520					525				
cag	ccg	gag	aac	aac	tac	aag	acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	1632
Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	
		530				535					540					
ggc	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	acc	gtg	gac	aag	agc	agg	tgg	1680
Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	
				550						555					560	
cag	cag	ggg	aac	gtc	ttc	tca	tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	1728
Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
				565					570					575		
aac	cac	tac	acg	cag	aag	agc	ctc	tcc	ctg	tct	ccg	ggt	aaa	tga		1773
Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys			
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 <213> Homo sapiens
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Val	Glu	Val	Glu	Ser	Phe	Leu	Val	His	Pro	Gly	Asp	Leu	Leu	Gln	Leu
			20					25					30		
Arg	Cys	Arg	Leu	Arg	Asp	Asp	Val	Gln	Ser	Ile	Asn	Trp	Leu	Arg	Asp
	35					40						45			
Gly	Val	Gln	Leu	Ala	Glu	Ser	Asn	Arg	Thr	Arg	Ile	Thr	Gly	Glu	Glu
	50					55					60				
Val	Glu	Val	Gln	Asp	Ser	Val	Pro	Ala	Asp	Ser	Gly	Leu	Tyr	Ala	Cys
65				70					75						80
Val	Thr	Ser	Ser	Pro	Ser	Gly	Ser	Asp	Thr	Thr	Tyr	Phe	Ser	Val	Asn

Val Ser Asp Ala₁₀₀ Leu Pro Ser Ser Glu₁₀₅ Asp Asp Asp Asp Asp₁₁₀ Asp Asp
 Ser Ser Ser₁₁₅ Glu Glu Lys Glu Thr₁₂₀ Asp Asn Thr Lys Pro₁₂₅ Asn Arg Met
 Pro Val₁₃₀ Ala Pro Tyr Trp Thr₁₃₅ Ser Pro Glu Lys Met₁₄₀ Glu Lys Lys Leu
 His₁₄₅ Ala Val Pro Ala₁₅₀ Ala Lys Thr Val Lys₁₅₅ Phe Lys Cys Pro Ser₁₆₀ Ser
 Gly Thr Pro Asn₁₆₅ Pro Thr Leu Arg Trp Leu₁₇₀ Lys Asn Gly Lys Glu₁₇₅ Phe
 Lys Pro Asp His₁₈₀ Arg Ile Gly Gly Tyr₁₈₅ Lys Val Arg Tyr Ala₁₉₀ Thr Trp
 Ser Ile Ile₁₉₅ Met Asp Ser Val₂₀₀ Val Pro Ser Asp Lys₂₀₅ Gly Asn Tyr Thr
 Cys Ile₂₁₀ Val Glu Asn Glu Tyr₂₁₅ Gly Ser Ile Asn His₂₂₀ Thr Tyr Gln Leu
 Asp Val₂₂₅ Val Glu Arg Ser₂₃₀ Pro His Arg Pro Ile₂₃₅ Leu Gln Ala Gly Leu₂₄₀
 Pro Ala Asn Lys₂₄₅ Thr Val Ala Leu Gly Ser₂₅₀ Asn Val Glu Phe Met₂₅₅ Cys
 Lys Val Tyr Ser₂₆₀ Asp Pro Gln Pro His₂₆₅ Ile Gln Trp Leu Lys₂₇₀ His Ile
 Glu Val Asn₂₇₅ Gly Ser Lys Ile Gly₂₈₀ Pro Asp Asn Leu Pro₂₈₅ Tyr Val Gln
 Ile Leu₂₉₀ Lys Thr Ala Gly Val₂₉₅ Asn Thr Thr Asp Lys₃₀₀ Glu Met Glu Val
 Leu His₃₀₅ Leu Arg Asn Val₃₁₀ Ser Phe Glu Asp Ala₃₁₅ Gly Glu Tyr Thr Cys₃₂₀
 Leu Ala Gly Asn₃₂₅ Ser Ile Gly Leu Ser His₃₃₀ His Ser Ala Trp Leu₃₃₅ Thr
 Val Leu Glu Ala₃₄₀ Leu Glu Glu Arg Pro Ala Val Met Thr Ser₃₅₀ Pro Leu
 Tyr Leu Glu Ile Ala Leu Glu Pro Lys Ser Cys Asp Lys Thr His Thr

355

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360 365Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
370 375 380Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
385 390 395 400Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
405 410 415Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
420 425 430Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
435 440 445Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
450 455 460Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
465 470 475 480Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
485 490 495Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
500 505 510Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
515 520 525Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
530 535 540Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
545 550 555 560Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
565 570 575Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
580 585 590

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 <212> DNA
 <213> Homo sapiens

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 <222> (1)..(1773)

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Arg	Pro	Ser	Phe	Ser	Leu	Val	Glu	Asp	Thr	Thr	Leu	Glu	Pro	Glu	Glu		
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cca	cca	acc	aaa	tac	caa	atc	tct	caa	cca	gaa	gtg	tac	gtg	gct	gca		96
Pro	Pro	Thr	Lys	Tyr	Gln	Ile	Ser	Gln	Pro	Glu	Val	Tyr	Val	Ala	Ala		
			20					25					30				
cca	ggg	gag	tcg	cta	gag	gtg	cgc	tgc	ctg	ttg	aaa	gat	gcc	gcc	gtg		144
Pro	Gly	Glu	Ser	Leu	Glu	Val	Arg	Cys	Leu	Leu	Lys	Asp	Ala	Ala	Val		
		35					40					45					
atc	agt	tgg	act	aag	gat	ggg	gtg	cac	ttg	ggg	ccc	aac	aat	agg	aca		192
Ile	Ser	Trp	Thr	Lys	Asp	Gly	Val	His	Leu	Gly	Pro	Asn	Asn	Arg	Thr		
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gtg	ctt	att	ggg	gag	tac	ttg	cag	ata	aag	ggc	gcc	acg	cct	aga	gac		240
Val	Leu	Ile	Gly	Glu	Tyr	Leu	Gln	Ile	Lys	Gly	Ala	Thr	Pro	Arg	Asp		
65					70					75				80			
tcc	ggc	ctc	tat	gct	tgt	act	gcc	agt	agg	act	gta	gac	agt	gaa	act		288
Ser	Gly	Leu	Tyr	Ala	Cys	Thr	Ala	Ser	Arg	Thr	Val	Asp	Ser	Glu	Thr		
				85					90					95			
tgg	tac	ttc	atg	gtg	aat	gtc	aca	gat	gcc	atc	tca	tcc	gga	gat	gat		336
Trp	Tyr	Phe	Met	Val	Asn	Val	Thr	Asp	Ala	Ile	Ser	Ser	Gly	Asp	Asp		
			100					105					110				
gag	gat	gac	acc	gat	ggc	gcg	gaa	gat	ttt	gtc	agt	gag	aac	agt	aac		384
Glu	Asp	Asp	Thr	Asp	Gly	Ala	Glu	Asp	Phe	Val	Ser	Glu	Asn	Ser	Asn		
		115					120					125					
aac	aag	aga	gca	cca	tac	tgg	acc	aac	aca	gaa	aag	atg	gaa	aag	cgg		432
Asn	Lys	Arg	Ala	Pro	Tyr	Trp	Thr	Asn	Thr	Glu	Lys	Met	Glu	Lys	Arg		
	130					135					140						
ctc	cat	gct	gtg	cct	gcg	gcc	aac	act	gtc	aag	ttt	cgc	tgc	cca	gcc		480
Leu	His	Ala	Val	Pro	Ala	Ala	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala		
145					150					155					160		
ggg	ggg	aac	cca	atg	cca	acc	atg	cgg	tgg	ctg	aaa	aac	ggg	aag	gag		528
Gly	Gly	Asn	Pro	Met	Pro	Thr	Met	Arg	Trp	Leu	Lys	Asn	Gly	Lys	Glu		
				165					170					175			
ttt	aag	cag	gag	cat	cgc	att	gga	ggc	tac	aag	gta	cga	aac	cag	cac		576
Phe	Lys	Gln	Glu	His	Arg	Ile	Gly	Gly	Tyr	Lys	Val	Arg	Asn	Gln	His		
			180					185					190				
tgg	agc	ctc	att	atg	gaa	agt	gtg	gtc	cca	tct	gac	aag	gga	aat	tat		624
Trp	Ser	Leu	Ile	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Lys	Gly	Asn	Tyr		
		195					200					205					
acc	tgt	gtg	gtg	gag	aat	gaa	tac	ggg	tcc	atc	aat	cac	acg	tac	cac		672
Thr	Cys	Val	Val	Glu	Asn	Glu	Tyr	Gly	Ser	Ile	Asn	His	Thr	Tyr	His		
	210					215					220						
ctg	gat	gtt	gtg	gag	cga	tcg	cct	cac	cgg	ccc	atc	ctc	caa	gcc	gga		720
Leu	Asp	Val	Val	Glu	Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly		
225					230					235					240		
ctg	ccg	gca	aat	gcc	tcc	aca	gtg	gtc	gga	gga	gac	gta	gag	ttt	gtc		768
Leu	Pro	Ala	Asn	Ala	Ser	Thr	Val	Val	Gly	Gly	Asp	Val	Glu	Phe	Val		
				245					250					255			
tgc	aag	gtt	tac	agt	gat	gcc	cag	ccc	cac	atc	cag	tgg	atc	aag	cac		816
Cys	Lys	Val	Tyr	Ser	Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Ile	Lys	His		

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260			265			270														
gtg Val	gaa Glu	aag Lys 275	aac Asn	ggc Gly	agt Ser	aaa Lys	tac Tyr 280	ggg Gly	ccc Pro	gac Asp	ggg Gly	ctg Leu 285	ccc Pro	tac Tyr	ctc Leu	864				
aag Lys	gtt Val 290	ctc Leu	aag Lys	gcc Ala	gcc Ala	ggt Gly 295	gtt Val	aac Asn	acc Thr	acg Thr	gac Asp 300	aaa Lys	gag Glu	att Ile	gag Glu	912				
gtt Val 305	ctc Leu	tat Tyr	att Ile	cgg Arg	aat Asn 310	gta Val	act Thr	ttt Phe	gag Glu	gac Asp 315	gct Ala	ggg Gly	gaa Glu	tat Tyr	acg Thr 320	960				
tgc Cys	ttg Leu	gcg Ala	ggg Gly	aat Asn 325	tct Ser	att Ile	ggg Gly	ata Ile	tcc Ser 330	ttt Phe	cac His	tct Ser	gca Ala	tgg Trp 335	ttg Leu	1008				
aca Thr	gtt Val	ctg Leu	cca Pro 340	gcg Ala	cct Pro	gga Gly	aga Arg	gaa Glu 345	aag Lys	gag Glu	att Ile	aca Thr	gct Ala 350	tcc Ser	cca Pro	1056				
gac Asp	tac Tyr	ctg Leu 355	tca Ser	gcg Ala	cta Leu	gag Glu	ccc Pro 360	aaa Lys	tct Ser	tgt Cys	gac Asp	aaa Lys 365	act Thr	cac His	aca Thr	1104				
tgc Cys	cca Pro 370	ccg Pro	tgc Cys	cca Pro	gca Ala	cct Pro 375	gaa Glu	ctc Leu	ctg Leu	ggg Gly	gga Gly 380	ccg Pro	tca Ser	gtc Val	ttc Phe	1152				
ctc Leu 385	ttc Phe	ccc Pro	cca Pro	aaa Lys	ccc Pro 390	aag Lys	gac Asp	acc Thr	ctc Leu	atg Met 395	atc Ile	tcc Ser	cgg Arg	acc Thr	cct Pro 400	1200				
gag Glu	gtc Val	aca Thr	tgc Cys	gtg Val 405	gtg Val	gtg Val	gac Asp	gtg Val	agc Ser 410	cac His	gaa Glu	gac Asp	cct Pro	gag Glu 415	gtc Val	1248				
aag Lys	ttc Phe	aac Asn	tgg Trp 420	tac Tyr	gtg Val	gac Asp	ggc Gly	gtg Val 425	gag Glu	gtg Val	cat His	aat Asn	gcc Ala 430	aag Lys	aca Thr	1296				
aag Lys	ccg Pro	cgg Arg 435	gag Glu	gag Glu	cag Gln	tac Tyr	aac Asn 440	agc Ser	acg Thr	tac Tyr	cgt Arg	gtg Val 445	gtc Val	agc Ser	gtc Val	1344				
ctc Leu	acc Thr 450	gtc Val	ctg Leu	cac His	cag Gln	gac Asp 455	tgg Trp	ctg Leu	aat Asn	ggc Gly	aag Lys 460	gag Glu	tac Tyr	aag Lys	tgc Cys	1392				
aag Lys 465	gtc Val	tcc Ser	aac Asn	aaa Lys	gcc Ala 470	ctc Leu	cca Pro	gcc Ala	ccc Pro	atc Ile 475	gag Glu	aaa Lys	acc Thr	atc Ile	tcc Ser 480	1440				
aaa Lys	gcc Ala	aaa Lys	ggg Gly	cag Gln 485	ccc Pro	cga Arg	gaa Glu	cca Pro	cag Gln 490	gtg Val	tac Tyr	acc Thr	ctg Leu	ccc Pro 495	cca Pro	1488				
tcc Ser	cgg Arg	gat Asp	gag Glu 500	ctg Leu	acc Thr	aag Lys	aac Asn	cag Gln 505	gtc Val	agc Ser	ctg Leu	acc Thr	tgc Cys 510	ctg Leu	gtc Val	1536				
aaa Lys	ggc Gly	ttc Phe 515	tat Tyr	ccc Pro	agc Ser	gac Asp	atc Ile 520	gcc Ala	gtg Val	gag Glu	tgg Trp	gag Glu 525	agc Ser	aat Asn	ggg Gly	1584				
cag Gln	ccg Pro	gag Glu	aac Asn	aac Asn	tac Tyr	aag Lys	acc Thr	acg Thr	cct Pro	ccc Pro	gtg Val	ctg Leu	gac Asp	tcc Ser	gac Asp	1632				

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530		535		540															
ggc tcc ttc ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg																			1680
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp																			
545					550				555										
cag cag ggg aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac																			1728
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His																			
				565					570										
aac cac tac acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga																			1773
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys																			
			580					585											

<210> 48
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<400> 48

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Pro Gly Glu Ser Leu Glu Val Arg Cys Leu Leu Lys Asp Ala Ala Val
 35 40 45

Ile Ser Trp Thr Lys Asp Gly Val His Leu Gly Pro Asn Asn Arg Thr
 50 55 60

Val Leu Ile Gly Glu Tyr Leu Gln Ile Lys Gly Ala Thr Pro Arg Asp
 65 70 75 80

Ser Gly Leu Tyr Ala Cys Thr Ala Ser Arg Thr Val Asp Ser Glu Thr
 85 90 95

Trp Tyr Phe Met Val Asn Val Thr Asp Ala Ile Ser Ser Gly Asp Asp
 100 105 110

Glu Asp Asp Thr Asp Gly Ala Glu Asp Phe Val Ser Glu Asn Ser Asn
 115 120 125

Asn Lys Arg Ala Pro Tyr Trp Thr Asn Thr Glu Lys Met Glu Lys Arg
 130 135 140

Leu His Ala Val Pro Ala Ala Asn Thr Val Lys Phe Arg Cys Pro Ala
 145 150 155 160

Gly Gly Asn Pro Met Pro Thr Met Arg Trp Leu Lys Asn Gly Lys Glu
 165 170 175

Phe Lys Gln Glu His Arg Ile Gly Gly Tyr Lys Val Arg Asn Gln His
 180 185 190

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Trp Ser Leu Ile Met Glu Ser Val Val Pro Ser Asp Lys Gly Asn Tyr
 195 200 205
 Thr Cys Val Val Glu Asn Glu Tyr Gly Ser Ile Asn His Thr Tyr His
 210 215 220
 Leu Asp Val Val Glu Arg Ser Pro His Arg Pro Ile Leu Gln Ala Gly
 225 230 235 240
 Leu Pro Ala Asn Ala Ser Thr Val Val Gly Gly Asp Val Glu Phe Val
 245 250 255
 Cys Lys Val Tyr Ser Asp Ala Gln Pro His Ile Gln Trp Ile Lys His
 260 265 270
 Val Glu Lys Asn Gly Ser Lys Tyr Gly Pro Asp Gly Leu Pro Tyr Leu
 275 280 285
 Lys Val Leu Lys Ala Ala Gly Val Asn Thr Thr Asp Lys Glu Ile Glu
 290 295 300
 Val Leu Tyr Ile Arg Asn Val Thr Phe Glu Asp Ala Gly Glu Tyr Thr
 305 310 315 320
 Cys Leu Ala Gly Asn Ser Ile Gly Ile Ser Phe His Ser Ala Trp Leu
 325 330 335
 Thr Val Leu Pro Ala Pro Gly Arg Glu Lys Glu Ile Thr Ala Ser Pro
 340 345 350
 Asp Tyr Leu Ser Ala Leu Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 355 360 365
 Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 370 375 380
 Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 385 390 395 400
 Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 405 410 415
 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 420 425 430
 Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 435 440 445
 Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 450 455 460

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Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
465 470 475 480

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
485 490 495

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
500 505 510

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
515 520 525

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
530 535 540

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
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Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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1							10					15							
ttc tcc ctt gag gcc tct gag gaa atg gaa cag gag ccc tgc cca gcc																			96
Phe Ser Leu 20					Ala Ser Glu Glu Met		Glu Gln Glu Pro Cys					Pro Ala							
							25					30							
cca atc tcg gag cag caa gag cag gtg ttg act gtg gcc ctt ggg cag																			144
Pro Ile Ser 35					Gln Gln Glu Gln Val		Leu Thr Val Ala Leu Gly Gln												
							40					45							
cct gtg cgg cta tgc tgt ggc cgc act gag cgt ggt cgt cat tgg tac																			192
Pro Val Arg 50					Leu Cys Cys Gly Arg		Thr Glu Arg Gly Arg					His Trp Tyr							
							55					60							
aag gag ggc agc cgt tta gca tct gct ggg aga gta cgg ggc tgg aga																			240
Lys Glu Gly Ser Arg 70					Leu Ala Ser Ala Gly		Arg Val Arg Gly Trp Arg												
65							75					80							
ggc cgc ctg gag atc gcc agc ttc ctt cct gag gat gct ggc cgg tac																			288
Gly Arg Leu Glu 85					Ile Ala Ser Phe Leu		Pro Glu Asp Ala Gly					Arg Tyr							
							90					95							

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Leu	Cys	Leu	Ala	Arg	Gly	Ser	Met	Thr	Val	Val	His	Asn	Leu	Thr	Leu	
			100					105					110			
att	atg	gat	gac	tcc	tta	ccc	tcc	atc	aat	aac	gag	gac	ccc	aag	acc	384
Ile	Met	Asp	Asp	Ser	Leu	Pro	Ser	Ile	Asn	Asn	Glu	Asp	Pro	Lys	Thr	
		115					120					125				
ctc	agc	agc	tcc	tcg	agt	ggg	cac	tcc	tac	ctg	cag	caa	gca	cct	tac	432
Leu	Ser	Ser	Ser	Ser	Ser	Gly	His	Ser	Tyr	Leu	Gln	Gln	Ala	Pro	Tyr	
	130					135					140					
tgg	aca	cac	ccc	caa	cgc	atg	gag	aag	aaa	ctg	cac	gcg	gta	cct	gcc	480
Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His	Ala	Val	Pro	Ala	
145					150					155					160	
ggg	aac	act	gtc	aaa	ttc	cgc	tgt	cca	gct	gca	ggg	aac	ccc	atg	ccc	528
Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly	Asn	Pro	Met	Pro	
				165				170						175		
acc	atc	cac	tgg	ctc	aag	aac	gga	cag	gcc	ttc	cac	gga	gag	aat	cgt	576
Thr	Ile	His	Trp	Leu	Lys	Asn	Gly	Gln	Ala	Phe	His	Gly	Glu	Asn	Arg	
			180					185					190			
atc	gga	ggc	att	cgg	ctg	cgt	cac	caa	cac	tgg	agc	ctc	gtg	atg	gag	624
Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser	Leu	Val	Met	Glu	
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agc	gtg	gtg	ccc	tca	gac	cgt	ggc	acg	tac	acg	tgt	ctt	gtg	gag	aac	672
Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys	Leu	Val	Glu	Asn	
	210					215					220					
tct	ctg	ggt	agc	att	cgc	tac	agc	tat	ctg	ctg	gat	gtg	ctg	gag	cgg	720
Ser	Leu	Gly	Ser	Ile	Arg	Tyr	Ser	Tyr	Leu	Leu	Asp	Val	Leu	Glu	Arg	
225					230					235					240	
tcc	ccg	cac	cgg	ccc	atc	ctg	cag	gcg	gga	ctc	cca	gcc	aac	acc	acg	768
Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Thr	Thr	
				245				250						255		
gct	gtg	gtt	ggc	agc	aac	gtg	gag	ctg	ctg	tgc	aag	gtg	tac	agt	gac	816
Ala	Val	Val	Gly	Ser	Asn	Val	Glu	Leu	Leu	Cys	Lys	Val	Tyr	Ser	Asp	
			260					265					270			
gcc	cag	ccg	cac	atc	cag	tgg	ctg	aag	cac	atc	gtt	atc	aac	ggc	agc	864
Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val	Ile	Asn	Gly	Ser	
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Pro Val Arg Leu Cys Cys Gly Arg Thr Glu Arg Gly Arg His Trp Tyr
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Lys Glu Gly Ser Arg Leu Ala Ser Ala Gly Arg Val Arg Gly Trp Arg
Page 46

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345

350

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cgg	ctg	tgc	tgt	ggg	cgg	gct	gag	cgt	ggt	ggc	cac	tgg	tac	aag	gag	144
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Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys	Leu	Val	Glu	Asn	Ala	
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Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val	Ile	Asn	Gly	Ser	Ser		
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 85 90 95
 agt ggt ccg gtg ttc ggc gga ggg acc aag ctg acc gtc cta ggt cag 336
 Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110
 ccc aag gct gcc ccc tcg gtc act ctg ttc ccg ccc tcc tct gag gag 384
 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125
 ctt caa gcc aac aag gcc aca ctg gtg tgt ctg atc agt gac ttc tac 432
 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140
 ccg gga gct gtg aca gtg gcc tgg aag gca gat ggc agc ccc gtc aag 480
 Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
 145 150 155 160
 gcg gga gtg gag acc acc aca ccc tcc aaa caa agc aac aac aag tac 528
 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175
 gcg gcc agc agc tat ctg agc ctg acg cct gag cag tgg aag tcc cac 576
 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190
 aga agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag aag 624
 Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205
 aca gtg gcc cct aca gaa tgt tca 648
 Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 72
 <211> 216
 <212> PRT
 <213> Homo sapiens

<400> 72

Gln Ser Glu Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
 1 5 10 15
 Arg Val Thr Ile Ser Cys Ser Gly Gly Tyr Ser Asn Met Gly Ser Asn
 20 25 30
 Tyr Ala His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45
 Ile Tyr Asn Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
 65 70 75 80
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
 85 90 95

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Ser Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145 150 155 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 73
<211> 9
<212> PRT
<213> Homo sapiens

<400> 73

Ser Asn Met Gly Ser Asn Tyr Ala His
1 5

<210> 74
<211> 5
<212> PRT
<213> Homo sapiens

<400> 74

Tyr Asn Asn Asn Gln
1 5

<210> 75
<211> 8
<212> PRT
<213> Homo sapiens

<400> 75

Ala Trp Asp Asp Ser Leu Ser Gly
1 5

<210> 76
<211> 411

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<212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(411)

<400> 76
 gaa gtt caa ttg tta gag tct ggt ggc ggt ctt gtt cag cct ggt ggt 48
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 tct tta cgt ctt tct tgc gct gct tcc gga ttc act ttc tct cct tac 96
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Pro Tyr
 20 25 30
 tgg atg ggt tgg gtt cgc caa gct cct ggt aaa ggt ttg gag tgg gtt 144
 Trp Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 tct gtt atc tgg cct tct ggt ggc act act gat tat gct gac tcc gtt 192
 Ser Val Ile Trp Pro Ser Gly Gly Thr Thr Asp Tyr Ala Asp Ser Val
 50 55 60
 aaa ggt cgc ttc act atc tct aga gac aac tct aag aat act ctc tac 240
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 ttg cag atg aac agc tta agg gct gag gac acg gcc gtg tat tac tgt 288
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 gcg aga gtc cat cca gct ggc cac aac gac cac tgg ggc cag gga acc 336
 Ala Arg Val His Pro Ala Gly His Asn Asp His Trp Gly Gln Gly Thr
 100 105 110
 ctg gtc acc gtc tca agc gcc tcc acc aag ggc cca tcg gtc ttc ccg 384
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 cta gca ccc tcc tcc aag agc acc tct 411
 Leu Ala Pro Ser Ser Lys Ser Thr Ser
 130 135

<210> 77
 <211> 137
 <212> PRT
 <213> Homo sapiens

<400> 77
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Pro Tyr
 20 25 30
 Trp Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Val Ile Trp Pro Ser Gly Gly Thr Thr Asp Tyr Ala Asp Ser Val
 50 55 60

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val His Pro Ala Gly His Asn Asp His Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135

<210> 78
<211> 9
<212> PRT
<213> Homo sapiens

<400> 78

Phe Thr Phe Ser Pro Tyr Trp Met Gly
1 5

<210> 79
<211> 10
<212> PRT
<213> Homo sapiens

<400> 79

Val Ile Trp Pro Ser Gly Gly Thr Thr Asp
1 5 10

<210> 80
<211> 10
<212> PRT
<213> Homo sapiens

<400> 80

Arg Val His Pro Ala Gly His Asn Asp His
1 5 10

<210> 81
<211> 645
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(645)

<400> 81
caa gac atc cag atg acc cag tct cca tcc tcc ctg tct ttg tct cca
Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Leu Ser Pro
1 5 10 15

48

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ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt att aac aga 96
 Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Arg
 20 25 30
 aac tta ggc tgg tac cag cag aag cct ggc cag gct ccc agg ctc ctc 144
 Asn Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35 40 45
 atc tat ggt gcg tcc acc agg gcc act ggt atc cca gcc agg ttc act 192
 Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Thr
 50 55 60
 ggc agt ggc tct ggc aca gag ttc tct ctc acc atc agc agc ctg cag 240
 Gly Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Gln
 65 70 75 80
 tct gaa gat tat gca att tat tat tgt cag cag tat gat aac tgg ccg 288
 Ser Glu Asp Tyr Ala Ile Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro
 85 90 95
 atc atc ttc ggc caa ggc aca cga ctg gag att aaa gga act gtg gct 336
 Ile Ile Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Gly Thr Val Ala
 100 105 110
 gca cca tct gtc ttc atc ttc ccg cca tct gat gag cag ttg aaa tct 384
 Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125
 gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc tat ccc aga gag 432
 Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
 130 135 140
 gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa tcg ggt aac tcc 480
 Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160
 cag gag agt gtc aca gag cag gac agc aag gac agc acc tac agc ctc 528
 Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
 165 170 175
 agc agc acc ctg acg ctg agc aaa gca gac tac gag aaa cac aaa gtc 576
 Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190
 tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg ccc gtc aca aag 624
 Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
 195 200 205
 agc ttc aac agg gga gag tgt 645
 Ser Phe Asn Arg Gly Glu Cys
 210 215

<210> 82
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 82

Gln Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Leu Ser Pro
 1 5 10 15

Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Arg
 20 25 30

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Asn Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Thr
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Tyr Ala Ile Tyr Tyr Cys Gln Gln Tyr Asp Asn Trp Pro
85 90 95

Ile Ile Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Gly Thr Val Ala
100 105 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 83
<211> 7
<212> PRT
<213> Homo sapiens

<400> 83

Ser Ile Asn Arg Asn Leu Gly
1 5

<210> 84
<211> 5
<212> PRT
<213> Homo sapiens

<400> 84

Tyr Gly Ala Ser Thr

1

5

<210> 85
 <211> 6
 <212> PRT
 <213> Homo sapiens

<400> 85

Gln Tyr Asp Asn Trp Pro
 1 5

<210> 86
 <211> 411
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(411)

<400> 86
 gaa gtt caa ttg tta gag tct ggt ggc ggt ctt gtt cag cct ggt ggt 48
 Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 tct tta cgt ctt tct tgc gct gct tcc gga ttc act ttc tct cgt tac 96
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
 20 25 30
 ttt atg aag tgg gtt cgc caa gct cct ggt aaa ggt ttg gag tgg gtt 144
 Phe Met Lys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 tct tgg atc tct cct tct ggt ggc ctt act gag tat gct gac tcc gtt 192
 Ser Trp Ile Ser Pro Ser Gly Gly Leu Thr Glu Tyr Ala Asp Ser Val
 50 55 60
 aaa ggt cgc ttc act atc tct aga gac aac tct aag aat act ctc tac 240
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 ttg cag atg aac agc tta agg gct gag gac acg gcc gtg tat tac tgt 288
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 gcc aga gcc tca tac ggt gcc tgg ctg gag tac tgg ggc cag ggc acc 336
 Ala Arg Ala Ser Tyr Gly Ala Trp Leu Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 ctg gtc acc gtc tca agc gcc tcc acc aag ggc cca tcg gtc ttc ccg 384
 Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
 115 120 125
 cta gca ccc tcc tcc aag agc acc tct 411
 Leu Ala Pro Ser Ser Lys Ser Thr Ser
 130 135

<210> 87
 <211> 137
 <212> PRT
 <213> Homo sapiens

<400> 87

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Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
20 25 30

Phe Met Lys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Trp Ile Ser Pro Ser Gly Gly Leu Thr Glu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Ser Tyr Gly Ala Trp Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135

<210> 88
<211> 9
<212> PRT
<213> Homo sapiens

<400> 88

Phe Thr Phe Ser Arg Tyr Phe Met Lys
1 5

<210> 89
<211> 10
<212> PRT
<213> Homo sapiens

<400> 89

Trp Ile Ser Pro Ser Gly Gly Leu Thr Glu
1 5 10

<210> 90
<211> 10
<212> PRT
<213> Homo sapiens

<400> 90

Arg Ala Ser Tyr Gly Ala Trp Leu Asp Tyr
1 5 10

<210> 91
 <211> 651
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(651)

<400> 91
 cag agc gtc ttg act cag cca ccc tca gcg tct ggg acc ccc ggc cag 48
 Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
 1 5 10 15
 ggg gtc acc atc tct tgt tct gga agc agc tcc aac atc gga agt aat 96
 Gly Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30
 agt gtt aac tgg tac cag cag ctc cca gga gcg gcc ccc aaa ctc ctc 144
 Ser Val Asn Trp Tyr Gln Gln Leu Pro Gly Ala Ala Pro Lys Leu Leu
 35 40 45
 atc tat agt aac aat ctg cgg ccc tca ggg gtc cct gcc cga ttc tct 192
 Ile Tyr Ser Asn Asn Leu Arg Pro Ser Gly Val Pro Ala Arg Phe Ser
 50 55 60
 ggc tcc aag tct ggc acc tca gcc tcc ctg gcc atc agt ggc ctc cgg 240
 Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg
 65 70 75 80
 tct gag gat gag gct gat tat tac tgt gca gcc tgg gat gac ggc ctg 288
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Gly Leu
 85 90 95
 gat gcc tat gtg gtg ttc ggc gga ggg acc aaa ctg acc gtc ctg ggt 336
 Asp Ala Tyr Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
 100 105 110
 cag ccc aag gcc aac ccc act gtc act ctg ttc ccg ccc tcc tct gag 384
 Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125
 gag ctc caa gcc aac aag gcc aca cta gtg tgt ctg atc agt gac ttc 432
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140
 tac ccg gga gct gtg aca gtg gcc tgg aag gca gat ggc agc ccc gtc 480
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val
 145 150 155 160
 aag gcg gga gtg gag acc acc aaa ccc tcc aaa cag agc aac aac aag 528
 Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175
 tac gcg gcc agc agc tac ctg agc ctg acg ccc gag cag tgg aag tcc 576
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190
 cac aga agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag 624
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205
 aag aca gtg gcc cct gca gaa tgc tct 651
 Lys Thr Val Ala Pro Ala Glu Cys Ser
 210 215

<210> 92
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 92

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

<210> 93
 <211> 9
 <212> PRT

<213> Homo sapiens

<400> 93

Ser Asn Ile Gly Ser Asn Ser Val Asn
1 5

<210> 94

<211> 5

<212> PRT

<213> Homo sapiens

<400> 94

Tyr Ser Asn Asn Leu
1 5

<210> 95

<211> 9

<212> PRT

<213> Homo sapiens

<400> 95

Ala Trp Asp Asp Gly Leu Asp Ala Tyr
1 5

<210> 96

<211> 414

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(414)

<400> 96

gaa gtt caa ttg tta gag tct ggt ggc ggt ctt gtt cag cct ggt ggt 48
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15tct tta cgt ctt tct tgc gct gct tcc gga ttc act ttc tct act tac 96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30tgg atg gct tgg gtt cgc caa gct cct ggt aaa ggt ttg gag tgg gtt 144
Trp Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45tct gtt atc ggt cct tct ggt ggc atg act gtt tat gct gac tcc gtt 192
Ser Val Ile Gly Pro Ser Gly Gly Met Thr Val Tyr Ala Asp Ser Val
50 55 60aaa ggt cgc ttc act atc tct aga gac aac tct aag aat act ctc tac 240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80ttg cag atg aac agc tta agg gct gag gac acg gcc gtg tat tac tgt 288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95gca cgg att aat agt ggg agc tcc cac ttt gac tac tgg ggc cag gga 336
Ala Arg Ile Asn Ser Gly Ser Ser His Phe Asp Tyr Trp Gly Gln Gly
100 105 110

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acc ctg gtc acc gtc tca agc gcc tcc acc aag ggc cca tcg gtc ttc 384
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

ccg cta gca ccc tcc tcc aag agc acc tct 414
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135

<210> 97
<211> 138
<212> PRT
<213> Homo sapiens

<400> 97

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Trp Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Val Ile Gly Pro Ser Gly Gly Met Thr Val Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ile Asn Ser Gly Ser Ser His Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
130 135

<210> 98
<211> 9
<212> PRT
<213> Homo sapiens

<400> 98

Phe Thr Phe Ser Thr Tyr Trp Met Ala
1 5

<210> 99
<211> 10
<212> PRT
<213> Homo sapiens

<400> 99

Val Ile Gly Pro Ser Gly Gly Met Thr Val
 1 5 10

<210> 100

<211> 11

<212> PRT

<213> Homo sapiens

<400> 100

Arg Ile Asn Ser Gly Ser Ser His Phe Asp Tyr
 1 5 10

<210> 101

<211> 651

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(651)

<400> 101

cag tac gaa ttg act cag cca ccc tca gcg tct ggg acc ccc ggg cag 48
 Gln Tyr Glu Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
 1 5 10 15

agg gtc acc atc tct tgt tct gga agc agc tcc aac atc gga agc aat 96
 Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30

att gta cac tgg tac cag cag ctg cca gga acg gcc ccc aaa ctg ctg 144
 Ile Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45

ata tat ggt aat aat cag cgg ccc tca ggg gtc cct gac cga ttc tct 192
 Ile Tyr Gly Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

gtc tcc aag tct ggc tcc tca gcc tcc ctg gcc atc agt ggg ctg cag 240
 Val Ser Lys Ser Gly Ser Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
 65 70 75 80

tct gag gat gag gct gat tat tac tgt gca tca tgg gat gac agc ctg 288
 Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Asp Asp Ser Leu
 85 90 95

aaa gcc ttt tat gtc ttc gga act ggg acc aag gtc acc gtc cta ggt 336
 Lys Ala Phe Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
 100 105 110

cag ccc aag gcc aac ccc act gtc act ctg ttc ccg ccc tcc tct gag 384
 Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125

gag ctg caa gcc aac aag gcc aca cta gtg tgt ctg atc agt gac ttc 432
 Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140

tac ccg gga gct gtg aca gtg gcc tgg aag gca gat ggc agc ccc gtc 480
 Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val
 145 150 155 160

pctfr2009051343-seq1

aag gcg gga gtg gag acc acc aaa ccc tcc aaa cag agc aac aac aag 528
 Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys
 165 170 175

tac gcg gcc agc agc tac ctg agc ctg acg ccc gag cag tgg aag tcc 576
 Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
 180 185 190

cac aga agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag 624
 His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
 195 200 205

aag aca gtg gcc cct aca gaa tgt tca 651
 Lys Thr Val Ala Pro Thr Glu Cys Ser
 210 215

<210> 102

<211> 217

<212> PRT

<213> Homo sapiens

<400> 102

Gln Tyr Glu Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
 1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
 20 25 30

Ile Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
 35 40 45

Ile Tyr Gly Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
 50 55 60

Val Ser Lys Ser Gly Ser Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
 65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Asp Asp Ser Leu
 85 90 95

Lys Ala Phe Tyr Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly
 100 105 110

Gln Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu
 115 120 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
 130 135 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val
 145 150 155 160

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

pctfr2009051343-seq1

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
180 185 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
195 200 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
210 215

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<400> 103

Ser Asn Ile Gly Ser Asn Ile Val His
1 5

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Tyr Gly Asn Asn Gln
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Ser Trp Asp Asp Ser Leu Lys Ala Phe
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1 5 10 15	
tct tta cgt ctt tct tgc gct gct tcc gga ttc act ttc tct cat tac	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr	
20 25 30	
tgg atg ggt tgg gtt cgc caa gct cct ggt aaa ggt ttg gag tgg gtt	144
Trp Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	

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tct gtt atc tct cct tct ggt ggc ctt act att tat gct gac tcc gtt	192
Ser Val Ile Ser Pro Ser Gly Gly Leu Thr Ile Tyr Ala Asp Ser Val	
50 55 60	
aaa ggt cgc ttc act atc tct aga gac aac tct aag aat act ctc tac	240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
ttg cag atg aac agc tta agg gct gag gac acg gcc gtg tat tac tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gca cgg agc agt ggc tgg gct ctg gat gct ttt gat atc tgg ggc caa	336
Ala Arg Ser Ser Gly Trp Ala Leu Asp Ala Phe Asp Ile Trp Gly Gln	
100 105 110	
ggg aca atg gtc acc gtc tca agc gcc tcc acc aag ggc cca tcg gtc	384
Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val	
115 120 125	
ttc ccg cta gca ccc tcc tcc aag agc acc tct ggg	420
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly	
130 135 140	

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Trp Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	
35 40 45	
Ser Val Ile Ser Pro Ser Gly Gly Leu Thr Ile Tyr Ala Asp Ser Val	
50 55 60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	
65 70 75 80	
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
Ala Arg Ser Ser Gly Trp Ala Leu Asp Ala Phe Asp Ile Trp Gly Gln	
100 105 110	
Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val	
115 120 125	
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly	
130 135 140	

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<210> 108
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Phe Thr Phe Ser His Tyr Trp Met Gly
 1 5

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<400> 109

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

<210> 110
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Arg Ser Ser Gly Trp Ala Leu Asp Ala Phe Asp Ile
 1 5 10

<210> 111
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 Met Arg Leu Leu 5 Ala Leu Leu Gly Val 10 Leu Leu Ser Val 15 Pro Gly
 1 5 10 15
 cct cca gtc ttg tcc ctg gag gcc tct gag gaa gtg gag ctt gag ccc 96
 Pro Pro Val Leu Ser Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro 20 25 30
 tgc ctg gct ccc agc ctg gag cag caa gag cag gag ctg aca gta gcc 144
 Cys Leu Ala Pro Ser Leu Glu Gln Gln Glu Gln Glu Leu Thr Val Ala 35 40 45
 ctt ggg cag cct gtg cgg ctg tgc tgt ggg cgg gct gag cgt ggt ggc 192
 Leu Gly Gln Pro Val Arg Leu Cys Cys Gly Arg Ala Glu Arg Gly Gly 50 55 60
 cac tgg tac aag gag ggc agt cgc ctg gca cct gct ggc cgt gta cgg 240
 His Trp Tyr Lys Glu Gly Ser Arg Leu Ala Pro Ala Gly Arg Val Arg 65 70 75 80
 ggc tgg agg ggc cgc cta gag att gcc agc ttc cta cct gag gat gct 288
 Gly Trp Arg Gly Arg Leu Glu Ile Ala Ser Phe Leu Pro Glu Asp Ala 85 90 95

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ggc Gly	cgc Arg	tac Tyr	ctc Leu 100	tgc Cys	ctg Leu	gca Ala	cga Arg	ggc Gly 105	tcc Ser	atg Met	atc Ile	gtc Val	ctg Leu 110	cag Gln	aat Asn	336
ctc Leu	acc Thr	ttg Leu 115	att Ile	aca Thr	ggt Gly	gac Asp	tcc Ser 120	ttg Leu	acc Thr	tcc Ser	agc Ser	aac Asn 125	gat Asp	gat Asp	gag Glu	384
gac Asp	ccc Pro 130	aag Lys	tcc Ser	cat His	agg Arg	gac Asp 135	ctc Leu	tcg Ser	aat Asn	agg Arg	cac His 140	agt Ser	tac Tyr	ccc Pro	cag Gln	432
caa Gln 145	gca Ala	ccc Pro	tac Tyr	tgg Trp	aca Thr 150	cac His	ccc Pro	cag Gln	cgc Arg	atg Met 155	gag Glu	aag Lys	aaa Lys	ctg Leu	cat His 160	480
gca Ala	gta Val	cct Pro	gcg Ala 165	ggg Gly	aac Asn	acc Thr	gtc Val	aag Lys	ttc Phe 170	cgc Arg	tgt Cys	cca Pro	gct Ala	gca Ala 175	ggc Gly	528
aac Asn	ccc Pro	acg Thr	aaa Lys 180	act Thr	cac His	aca Thr	tgc Cys	cca Pro 185	ccg Pro	tgc Cys	cca Pro	gca Ala	cct Pro 190	gaa Glu	ctc Leu	576
ctg Leu	ggg Gly	gga Gly 195	ccg Pro	tca Ser	gtc Val	ttc Phe	ctc Leu 200	ttc Phe	ccc Pro	cca Pro	aaa Lys	ccc Pro 205	aag Lys	gac Asp	acc Thr	624
ctc Leu	atg Met 210	atc Ile	tcc Ser	cgg Arg	acc Thr	cct Pro 215	gag Glu	gtc Val	aca Thr	tgc Cys	gtg Val 220	gtg Val	gtg Val	gac Asp	gtg Val	672
agc Ser 225	cac His	gaa Glu	gac Asp	cct Pro	gag Glu 230	gtc Val	aag Lys	ttc Phe	aac Asn	tgg Trp 235	tac Tyr	gtg Val	gac Asp	ggc Gly	gtg Val 240	720
gag Glu	gtg Val	cat His	aat Asn	gcc Ala 245	aag Lys	aca Thr	aag Lys	ccg Pro 250	cgg Arg	gag Glu	gag Glu	cag Gln	tac Tyr	aac Asn 255	agc Ser	768
acg Thr	tac Tyr	cgt Arg	gtg Val 260	gtc Val	agc Ser	gtc Val	ctc Leu	acc Thr 265	gtc Val	ctg Leu	cac His	cag Gln	gac Asp 270	tgg Trp	ctg Leu	816
aat Asn	ggc Gly	aag Lys 275	gag Glu	tac Tyr	aag Lys	tgc Cys	aag Lys 280	gtc Val	tcc Ser	aac Asn	aaa Lys	gcc Ala 285	ctc Leu	cca Pro	gcc Ala	864
ccc Pro	atc Ile 290	gag Glu	aaa Lys	acc Thr	atc Ile	tcc Ser 295	aaa Lys	gcc Ala	aaa Lys	ggg Gly	cag Gln 300	ccc Pro	cga Arg	gaa Glu	cca Pro	912
cag Gln 305	gtg Val	tac Tyr	acc Thr	ctg Leu	ccc Pro 310	cca Pro	tcc Ser	cgg Arg	gat Asp	gag Glu 315	ctg Leu	acc Thr	aag Lys	aac Asn	cag Gln 320	960
gtc Val	agc Ser	ctg Leu	acc Thr	tgc Cys 325	ctg Leu	gtc Val	aaa Lys	ggc Gly	ttc Phe 330	tat Tyr	ccc Pro	agc Ser	gac Asp	atc Ile 335	gcc Ala	1008
gtg Val	gag Glu	tgg Trp	gag Glu 340	agc Ser	aat Asn	ggg Gly	cag Gln 345	ccg Pro	gag Glu	aac Asn	aac Asn	tac Tyr	aag Lys 350	acc Thr	acg Thr	1056
cct Pro	ccc Pro	gtg Val 355	ctg Leu	gac Asp	tcc Ser	gac Asp	ggc Gly 360	tcc Ser	ttc Phe	ttc Phe	ctc Leu	tac Tyr 365	agc Ser	aag Lys	ctc Leu	1104

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acc	gtg	gac	aag	agc	agg	tgg	cag	cag	ggg	aac	gtc	ttc	tca	tgc	tcc	1152
Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	
	370					375					380					
gtg	atg	cat	gag	gct	ctg	cac	aac	cac	tac	acg	cag	aag	agc	ctc	tcc	1200
Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	
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ctg	tct	ccg	ggt	tga												1215
Leu	Ser	Pro	Gly													

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<400> 112

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

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

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
210 215 220

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
225 230 235 240

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
245 250 255

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
260 265 270

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
275 280 285

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
290 295 300

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
305 310 315 320

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
325 330 335

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
340 345 350

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
355 360 365

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
370 375 380

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
385 390 395 400

Leu Ser Pro Gly

<210> 113
<211> 1068
<212> DNA
<213> Homo sapiens

<220>
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<400> 113

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1 5 10 15	
cct cca gtc ttg tcc ctg gag gcc tct gag gaa gtg gag ctt gag ccc	96
Pro Pro Val Leu Ser Leu Glu Ala Ser Glu Glu Val Glu Leu Glu Pro	
20 25 30	
caa gca ccc tac tgg aca cac ccc cag cgc atg gag aag aaa ctg cat	144
Gln Ala Pro Tyr Trp Thr His Pro Gln Arg Met Glu Lys Lys Leu His	
35 40 45	
gca gta cct gcg ggg aac acc gtc aag ttc cgc tgt cca gct gca ggc	192
Ala Val Pro Ala Gly Asn Thr Val Lys Phe Arg Cys Pro Ala Ala Gly	
50 55 60	
aac ccc acg ccc acc atc cgc tgg ctt aag gat gga cag gcc ttt cat	240
Asn Pro Thr Pro Thr Ile Arg Trp Leu Lys Asp Gly Gln Ala Phe His	
65 70 75 80	
ggg gag aac cgc att gga ggc att cgg ctg cgc cat cag cac tgg agt	288
Gly Glu Asn Arg Ile Gly Gly Ile Arg Leu Arg His Gln His Trp Ser	
85 90 95	
ctc gtg atg gag agc gtg gtg ccc tcg gac cgc ggc aca tac acc tgc	336
Leu Val Met Glu Ser Val Val Pro Ser Asp Arg Gly Thr Tyr Thr Cys	
100 105 110	
ctg gta gag aac gct gtg ggc agc atc cgt tat aac tac ctg cta gat	384
Leu Val Glu Asn Ala Val Gly Ser Ile Arg Tyr Asn Tyr Leu Leu Asp	
115 120 125	
gtg ctg aaa act cac aca tgc cca ccg tgc cca gca cct gaa ctc ctg	432
Val Leu Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu	
130 135 140	
ggg gga ccg tca gtc ttc ctc ttc ccc cca aaa ccc aag gac acc ctc	480
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu	
145 150 155 160	
atg atc tcc cgg acc cct gag gtc aca tgc gtg gtg gtg gac gtg agc	528
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser	
165 170 175	
cac gaa gac cct gag gtc aag ttc aac tgg tac gtg gac ggc gtg gag	576
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu	
180 185 190	
gtg cat aat gcc aag aca aag ccg cgg gag gag cag tac aac agc acg	624
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr	
195 200 205	
tac cgt gtg gtc agc gtc ctc acc gtc ctg cac cag gac tgg ctg aat	672
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn	
210 215 220	
ggc aag gag tac aag tgc aag gtc tcc aac aaa gcc ctc cca gcc ccc	720
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro	
225 230 235 240	
atc gag aaa acc atc tcc aaa gcc aaa ggg cag ccc cga gaa cca cag	768
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln	
245 250 255	
gtg tac acc ctg ccc cca tcc cgg gat gag ctg acc aag aac cag gtc	816
Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val	
260 265 270	

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agc	ctg	acc	tgc	ctg	gtc	aaa	ggc	ttc	tat	ccc	agc	gac	atc	gcc	gtg	864
Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	
		275					280					285				
gag	tgg	gag	agc	aat	ggg	cag	ccg	gag	aac	aac	tac	aag	acc	acg	cct	912
Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	
	290					295					300					
ccc	gtg	ctg	gac	tcc	gac	ggc	tcc	ttc	ttc	ctc	tac	agc	aag	ctc	acc	960
Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	
305					310					315					320	
gtg	gac	aag	agc	agg	tgg	cag	cag	ggg	aac	gtc	ttc	tca	tgc	tcc	gtg	1008
Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	
				325				330						335		
atg	cat	gag	gct	ctg	cac	aac	cac	tac	acg	cag	aag	agc	ctc	tcc	ctg	1056
Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	
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tct	ccg	ggg	tga													1068
Ser	Pro	Gly														
		355														

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<400> 114

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			20					25					30		
Gln	Ala	Pro	Tyr	Trp	Thr	His	Pro	Gln	Arg	Met	Glu	Lys	Lys	Leu	His
		35					40					45			
Ala	Val	Pro	Ala	Gly	Asn	Thr	Val	Lys	Phe	Arg	Cys	Pro	Ala	Ala	Gly
	50					55					60				
Asn	Pro	Thr	Pro	Thr	Ile	Arg	Trp	Leu	Lys	Asp	Gly	Gln	Ala	Phe	His
65					70					75				80	
Gly	Glu	Asn	Arg	Ile	Gly	Gly	Ile	Arg	Leu	Arg	His	Gln	His	Trp	Ser
				85					90					95	
Leu	Val	Met	Glu	Ser	Val	Val	Pro	Ser	Asp	Arg	Gly	Thr	Tyr	Thr	Cys
			100					105					110		
Leu	Val	Glu	Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp
		115					120					125			
Val	Leu	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
	130					135					140				

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Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
145 150 155 160

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
165 170 175

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
180 185 190

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
195 200 205

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
210 215 220

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

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
245 250 255

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
260 265 270

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
275 280 285

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
290 295 300

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
305 310 315 320

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
325 330 335

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
340 345 350

Ser Pro Gly
355

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<220>
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<400> 115
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cct	cca	gtc	ttg	tcc	ctg	gag	gcc	tct	gag	gaa	gtg	gag	ctt	gag	ccc	96
Pro	Pro	Val	Leu	Ser	Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro	
			20					25					30			
aac	gct	gtg	ggc	agc	atc	cgt	tat	aac	tac	ctg	cta	gat	gtg	ctg	gag	144
Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp	Val	Leu	Glu	
		35					40					45				
cgg	tcc	ccg	cac	cgg	ccc	atc	ctg	cag	gcc	ggg	ctc	ccg	gcc	aac	acc	192
Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Thr	
		50				55					60					
aca	gcc	gtg	gtg	ggc	agc	gac	gtg	gag	ctg	ctg	tgc	aag	gtg	tac	agc	240
Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys	Val	Tyr	Ser	
65				70				75							80	
gat	gcc	cag	ccc	cac	atc	cag	tgg	ctg	aag	cac	atc	gtc	atc	aac	ggc	288
Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val	Ile	Asn	Gly	
				85				90						95		
agc	agc	ttc	gga	gcc	gac	ggt	ttc	ccc	tat	gtg	caa	gtc	cta	aag	act	336
Ser	Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val	Leu	Lys	Thr	
			100					105					110			
gca	gac	atc	aat	agc	tca	gag	gtg	gag	gtc	ctg	tac	ctg	cgg	aac	gtg	384
Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu	Arg	Asn	Val	
		115				120						125				
tca	gcc	gag	gac	gca	ggc	gag	tac	acc	tgc	ctc	gca	ggc	aat	tcc	atc	432
Ser	Ala	Glu	Asp	Ala	Gly	Glu	Tyr	Thr	Cys	Leu	Ala	Gly	Asn	Ser	Ile	
		130				135					140					
ggc	ctc	tcc	tac	cag	tct	gcc	tgg	ctc	acg	gtg	ctg	cca	gag	gag	gac	480
Gly	Leu	Ser	Tyr	Gln	Ser	Ala	Trp	Leu	Thr	Val	Leu	Pro	Glu	Glu	Asp	
145				150						155					160	
ccc	aca	tgg	acc	gca	gca	gcg	ccc	gag	gcc	aaa	act	cac	aca	tgc	cca	528
Pro	Thr	Trp	Thr	Ala	Ala	Ala	Pro	Glu	Ala	Lys	Thr	His	Thr	Cys	Pro	
				165				170						175		
ccg	tgc	cca	gca	cct	gaa	ctc	ctg	ggg	gga	ccg	tca	gtc	ttc	ctc	ttc	576
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	
			180					185					190			
ccc	cca	aaa	ccc	aag	gac	acc	ctc	atg	atc	tcc	cgg	acc	cct	gag	gtc	624
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	
		195					200					205				
aca	tgc	gtg	gtg	gtg	gac	gtg	agc	cac	gaa	gac	cct	gag	gtc	aag	ttc	672
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	
		210				215					220					
aac	tgg	tac	gtg	gac	ggc	gtg	gag	gtg	cat	aat	gcc	aag	aca	aag	ccg	720
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	
225				230						235					240	
cgg	gag	gag	cag	tac	aac	agc	acg	tac	cgt	gtg	gtc	agc	gtc	ctc	acc	768
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	
				245				250						255		
gtc	ctg	cac	cag	gac	tgg	ctg	aat	ggc	aag	gag	tac	aag	tgc	aag	gtc	816
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	
			260					265					270			
tcc	aac	aaa	gcc	ctc	cca	gcc	ccc	atc	gag	aaa	acc	atc	tcc	aaa	gcc	864

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Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala		
		275					280					285					
aaa	ggg	cag	ccc	cga	gaa	cca	cag	gtg	tac	acc	ctg	ccc	cca	tcc	cgg		912
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr		300	Pro	Pro	Ser	Arg	
	290					295											
gat	gag	ctg	acc	aag	aac	cag	gtc	agc	ctg	acc	tgc	ctg	gtc	aaa	ggc		960
Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly		
305					310					315					320		
ttc	tat	ccc	agc	gac	atc	gcc	gtg	gag	tgg	gag	agc	aat	ggg	cag	ccg		1008
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro		
				325					330					335			
gag	aac	aac	tac	aag	acc	acg	cct	ccc	gtg	ctg	gac	tcc	gac	ggc	tcc		1056
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser		
			340					345					350				
ttc	ttc	ctc	tac	agc	aag	ctc	acc	gtg	gac	aag	agc	agg	tgg	cag	cag		1104
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln		
		355					360					365					
ggg	aac	gtc	ttc	tca	tgc	tcc	gtg	atg	cat	gag	gct	ctg	cac	aac	cac		1152
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His		
	370					375					380						
tac	acg	cag	aag	agc	ctc	tcc	ctg	tct	ccg	ggt	tga						1188
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly							
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 <212> PRT
 <213> Homo sapiens
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Pro	Pro	Val	Leu	Ser	Leu	Glu	Ala	Ser	Glu	Glu	Val	Glu	Leu	Glu	Pro		
			20					25					30				
Asn	Ala	Val	Gly	Ser	Ile	Arg	Tyr	Asn	Tyr	Leu	Leu	Asp	Val	Leu	Glu		
		35					40					45					
Arg	Ser	Pro	His	Arg	Pro	Ile	Leu	Gln	Ala	Gly	Leu	Pro	Ala	Asn	Thr		
	50					55					60						
Thr	Ala	Val	Val	Gly	Ser	Asp	Val	Glu	Leu	Leu	Cys	Lys	Val	Tyr	Ser		
65					70				75					80			
Asp	Ala	Gln	Pro	His	Ile	Gln	Trp	Leu	Lys	His	Ile	Val	Ile	Asn	Gly		
				85					90					95			
Ser	Ser	Phe	Gly	Ala	Asp	Gly	Phe	Pro	Tyr	Val	Gln	Val	Leu	Lys	Thr		
			100					105					110				
Ala	Asp	Ile	Asn	Ser	Ser	Glu	Val	Glu	Val	Leu	Tyr	Leu	Arg	Asn	Val		

385

390

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<212> PRT
<213> Homo sapiens

<400> 117

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

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

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

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Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330