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(54) **PHARMACEUTICAL COMPOSITION FOR TREATMENT AND/OR PREVENTION OF PANCREATIC CANCER**

PHARMAZEUTISCHE ZUSAMMENSETZUNG ZUR BEHANDLUNG UND/ODER PRÄVENTION VON PANKREASKARZINOM

COMPOSITION PHARMACEUTIQUE DESTINÉE AU TRAITEMENT ET/OU À LA PRÉVENTION DU CANCER DU PANCRÉAS

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**EP 2 740 489 B1**

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**Description**

## Technical Field

5 **[0001]** The present invention relates to novel use of an antibody against CAPRIN-1 or a fragment thereof in a medicament such as a therapeutic agent for pancreatic cancer.

## Background Art

10 **[0002]** Cancer is the leading cause of death. This disease is currently treated principally by surgical therapy in combination with radiation therapy and/or chemotherapy. In spite of recent development of novel surgical techniques or discovery of novel anticancer agents, the existing treatment of cancer has an insufficiently improved outcome, except for some cancer types. With recent advances of molecular biology or cancer immunology, antibodies that specifically react with cancer, cancer antigens that are recognized by cytotoxic T cells, genes encoding such cancer antigens, and the like have been identified, raising expectations on specific cancer therapy targeting the cancer antigens (Non Patent Literature 1).

15 **[0003]** For reducing the adverse effect of cancer therapy, it is desired that peptides, polypeptides, or proteins recognized as antigens of the cancer should rarely exist in normal cells and specifically exist in cancer cells. In 1991, Boon et al. (Ludwig Institute for Cancer Research, Belgium) isolated a human melanoma antigen MAGE1 recognized by CD8-positive T cells by a cDNA expression cloning method using autologous cancer cell lines and cancer-reactive T cells (Non Patent Literature 2). Then, a SEREX (serological identification of antigens by recombinant expression cloning) method has been reported, which adopts a gene expression cloning approach to identify tumor antigens recognized by antibodies produced in response to autologous cancer *in vivo* in a cancer patient (Non Patent Literature 3 and Patent Literature 1). According to this method, some cancer antigens that are rarely expressed in normal cells and are specifically expressed in cancer have been isolated (Non Patent Literatures 4 to 9). In addition, cell therapy using immunocytes that specifically react with cancer antigens or cancer-specific immunotherapy using vaccines or the like comprising cancer antigens is under clinical trial targeting some of the isolated cancer antigens.

20 **[0004]** In recent years, various antibody drugs for cancer treatment targeting antigenic proteins on cancer cells have emerged in the world. These drugs have received attention because of their certain efficacy as cancer-specific therapeutic agents. A large majority of antigenic proteins targeted by the drugs, however, are also expressed in normal cells. As a result of administering the antibodies, cancer cells as well as normal cells expressing the antigens are damaged, disadvantageously resulting in adverse effects. Thus, if cancer antigens specifically expressed on the surface of cancer cells can be identified and antibodies targeting the antigens can be used as drugs, these antibody drugs can be expected to achieve treatment with less adverse effects. In terms of the technical common sense of those skilled in the art, pancreatic cancer is known to be difficult to treat. An effective drug having sufficient effects on pancreatic cancer has not yet been developed.

25 **[0005]** Cytoplasmic- and proliferation-associated protein 1 (CAPRIN-1) has been known as an intracellular protein that is expressed upon activation or cell division of resting normal cells and forms cytoplasmic stress granules with intracellular RNAs to participate in the regulation of transport and translation of mRNAs. This protein has been found to be specifically expressed on the surface of cancer cells such as breast cancer cells and is therefore under study as a target of antibody drugs for cancer treatment (Patent Literature 2). Patent Literature 2, however, did not confirm that CAPRIN-1 is expressed on pancreatic cancer cells, and neither disclosed nor suggested that CAPRIN-1 can serve as an antigenic protein for pancreatic cancer.

## 45 Prior Art Literatures

## Patent Literature

**[0006]**

50 Patent Literature 1: U.S. Patent No. 5698396  
Patent Literature 2: International Publication No. WO2010/016526

## Non Patent Literature

55 **[0007]**

Non Patent Literature 1: Tsuyoshi Akiyoshi, "Japanese Journal of Cancer and Chemotherapy", 1997, Vol. 24, p.

551-519 (Japanese Journal of Cancer and Chemotherapy Publishers Inc., Japan)

Non Patent Literature 2: Bruggen P. et al., Science, 254: 1643-1647 (1991)

Non Patent Literature 3: Proc. Natl. Acad. Sci. USA, 92: 11810-11813 (1995)

Non Patent Literature 4: Int. J. Cancer, 72: 965-971 (1997)

Non Patent Literature 5: Cancer Res., 58: 1034-1041 (1998)

Non Patent Literature 6: Int. J. Cancer, 29: 652-658 (1998)

Non Patent Literature 7: Int. J. Oncol., 14: 703-708 (1999)

Non Patent Literature 8: Cancer Res., 56: 4766-4772 (1996)

Non Patent Literature 9: Hum. Mol. Genet., 6: 33-39 (1997)

## Summary of Invention

### Problem to be Solved by the Invention

**[0008]** An object of the present invention is to identify a cancer antigenic protein specifically expressed on the surface of pancreatic cancer cells and provide use of an antibody targeting the protein as a therapeutic agent for pancreatic cancer.

### Means for Solving the Problem

**[0009]** As a result of conducting diligent studies, the present inventors have obtained a cDNA encoding a protein specifically binding to an antibody present in serum derived from a cancer-bearing organism, by the SEREX method using a canine testicular tissue-derived cDNA library and the serum of a breast cancer-affected dog, and then prepared CAPRIN-1 having an amino acid sequence represented by any of even-numbered SEQ ID NOs: 2 to 30, and a large number of antibodies against these CAPRIN-1 proteins, on the basis of the obtained gene and human, bovine, horse, mouse, and chicken homologous genes thereof. Then, the present inventors have now found that CAPRIN-1 protein segments are specifically expressed on the surface of pancreatic cancer cells, and also found that an antibody against CAPRIN-1 damages pancreatic cancer cells expressing CAPRIN-1. On the basis of these findings, the present invention has been completed.

**[0010]** Thus, the present invention has the following aspects: The present invention provides a pharmaceutical composition for use in a method of treatment of pancreatic cancer, comprising, as an active ingredient, an antibody or a fragment thereof which specifically has immunological reactivity with a CAPRIN-1 protein or a fragment thereof comprising 7 to 12 or more consecutive amino acid residues.

**[0011]** In an embodiment, the CAPRIN-1 protein has an amino acid sequence represented by any of even-numbered SEQ ID NOs: 2 to 30, or an amino acid sequence having 80% or higher, preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher, far more preferably 97 to 99% or higher sequence identity to the amino acid sequence.

**[0012]** In another embodiment, the antibody is a monoclonal antibody or a polyclonal antibody.

**[0013]** In a further embodiment, the antibody is a human antibody, a humanized antibody, a chimeric antibody, a single-chain antibody, or a multispecific antibody.

**[0014]** In a further embodiment, the antibody is an antibody having immunological reactivity with a polypeptide having an amino acid sequence represented by SEQ ID NO: 273, 266, 270, 272, or 269, or an amino acid sequence having 80% or higher, preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher, far more preferably 97 to 99% or higher sequence identity to the amino acid sequence, or a fragment thereof.

**[0015]** In a further embodiment, the antibody is any of the following antibodies (a) to (y) and has immunological reactivity with the CAPRIN-1 protein, or the pharmaceutical composition is for treatment and/or prevention of pancreatic cancer and is characterized by comprising the antibody as an effective ingredient:

(a) an antibody comprising a heavy chain variable region comprising complementarity determining regions (CDRs) of SEQ ID NOs: 37, 38, and 39 and a light chain variable region comprising CDRs of SEQ ID NOs: 41, 42, and 43;

(b) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 47, 48, and 49 and a light chain variable region comprising CDRs of SEQ ID NOs: 51, 52, and 53;

(c) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 57, 58, and 59 and a light chain variable region comprising CDRs of SEQ ID NOs: 61, 62, and 63;

(d) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 67, 68, and 69 and a light chain variable region comprising CDRs of SEQ ID NOs: 71, 72, and 73;

(e) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 77, 78, and 79 and a light chain variable region comprising CDRs of SEQ ID NOs: 81, 82, and 83;

(f) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 87, 88, and 89 and a

light chain variable region comprising CDRs of SEQ ID NOs: 91, 92, and 93;

(g) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 97, 98, and 99 and a light chain variable region comprising CDRs of SEQ ID NOs: 101, 102, and 103;

(h) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 107, 108, and 109 and a light chain variable region comprising CDRs of SEQ ID NOs: 111, 112, and 113;

(i) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 117, 118, and 119 and a light chain variable region comprising CDRs of SEQ ID NOs: 121, 122, and 123;

(j) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 127, 128, and 129 and a light chain variable region comprising CDRs of SEQ ID NOs: 131, 132, and 133;

(k) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 132, 133, and 134 and a light chain variable region comprising CDRs of SEQ ID NOs: 136, 137, and 138;

(l) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 142, 143, and 144 and a light chain variable region comprising CDRs of SEQ ID NOs: 146, 147, and 148;

(m) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 142, 143, and 144 and a light chain variable region comprising CDRs of SEQ ID NOs: 152, 153, and 154;

(n) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 157, 158, and 159 and a light chain variable region comprising CDRs of SEQ ID NOs: 161, 162, and 163;

(o) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 171, 172, and 173;

(p) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 177, 178, and 179;

(q) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 182, 183, and 184;

(r) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 187, 188, and 189;

(s) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 192, 193, and 194;

(t) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 197, 198, and 199 and a light chain variable region comprising CDRs of SEQ ID NOs: 201, 202, and 203;

(u) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 207, 208, and 209 and a light chain variable region comprising CDRs of SEQ ID NOs: 211, 212, and 213;

(v) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 217, 218, and 219 and a light chain variable region comprising CDRs of SEQ ID NOs: 221, 222, and 223;

(w) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 227, 228, and 229 and a light chain variable region comprising CDRs of SEQ ID NOs: 231, 232, and 233;

(x) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 237, 238, and 239 and a light chain variable region comprising CDRs of SEQ ID NOs: 241, 242, and 243; and

(y) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 247, 248, and 249 and a light chain variable region comprising CDRs of SEQ ID NOs: 251, 252, and 253.

**[0016]** In a further embodiment of the present invention, the antibody or the fragment thereof is conjugated with an antitumor agent.

**[0017]** The present invention further provides a pharmaceutical combination comprising the pharmaceutical composition of the present invention and a pharmaceutical composition comprising an antitumor agent.

**[0018]** The antibody against CAPRIN-1 used in the present invention damages pancreatic cancer cells. Thus, the antibody against CAPRIN-1 is useful in the treatment of pancreatic cancer.

#### Modes for Carrying Out the Invention

**[0019]** The antibody against a CAPRIN-1 protein, specifically, a polypeptide having an amino acid sequence represented by any of even-numbered SEQ ID NOs: 2 to 30, used in the present invention can be evaluated for its antitumor activity, as described later, by *examining in vivo* the inhibition of tumor growth in a cancer-bearing animal or by *examining ex vivo* the presence or absence of immunocyte- or complement-mediated cytotoxic activity exhibited by the antibody against tumor cells expressing the polypeptide.

**[0020]** The nucleotide sequences of polynucleotides encoding proteins consisting of amino acid sequences represented by even-numbered SEQ ID NOs (i.e., SEQ ID NOs: 2, 4, 6, ..., 28, and 30) of SEQ ID NOs: 2 to 30 are shown in odd-numbered SEQ ID NOs (i.e., SEQ ID NOs: 1, 3, 5, ..., 27, and 29) of SEQ ID NOs: 1 to 29, respectively.

**[0021]** The amino acid sequences represented by SEQ ID NOs: 6, 8, 10, 12, and 14 in the Sequence Listing are amino

acid sequences of CAPRIN-1 isolated as polypeptides specifically binding to antibodies present in serum derived from a cancer-bearing dog; the amino acid sequences represented by SEQ ID NOs: 2 and 4 are amino acid sequences of CAPRIN-1 isolated as human homologous factors (homologs or orthologs) thereof; the amino acid sequence represented by SEQ ID NO: 16 is an amino acid sequence of CAPRIN-1 isolated as a bovine homologous factor thereof; the amino acid sequence represented by SEQ ID NO: 18 is an amino acid sequence of CAPRIN-1 isolated as a horse homologous factor thereof; the amino acid sequences represented by SEQ ID NOs: 20 to 28 are amino acid sequences of CAPRIN-1 isolated as mouse homologous factors thereof; and the amino acid sequence represented by SEQ ID NO: 30 is an amino acid sequence of CAPRIN-1 isolated as a chicken homologous factor thereof (see Example 1 described later). CAPRIN-1 is known to be expressed upon activation or cell division of resting normal cells.

**[0022]** The study of the present invention has revealed that CAPRIN-1 protein is expressed on the surface of pancreatic cancer cells. According to the present invention, an antibody binding to a portion expressed on the surface of pancreatic cancer cells in each CAPRIN-1 protein molecule is preferably used. Examples of the partial peptide of the CAPRIN-1 protein expressed on the surface of pancreatic cancer cells include polypeptides each consisting of 7 to 12 or more, for example, 8 to 11 or more, consecutive amino acid residues in a region of amino acid residue numbers (aa) 50 to 98, amino acid residue numbers (aa) 233 to 343, or amino acid residue number (aa) 527 to the C terminus of an amino acid sequence represented by any even number (except for SEQ ID NOs: 6 and 18) of SEQ ID NOs: 2 to 30 in the Sequence Listing, and specifically include: an amino acid sequence represented by SEQ ID NO: 271 or 273 (preferably, for example, a region of an amino acid sequence represented by SEQ ID NO: 274 or 275 in the amino acid sequence represented by SEQ ID NO: 273); an amino acid sequence represented by SEQ ID NO: 266 (preferably, for example, a region of an amino acid sequence represented by SEQ ID NO: 267 or 268 in the amino acid sequence represented by SEQ ID NO: 266), 270, 272, or 269 as a partial peptide of the CAPRIN-1 protein expressed on the surface of cancer cells; and an amino acid sequence having 80% or higher, preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher, for example, 96% or higher, 97% or higher, 98% or higher, or 99% or higher sequence identity to any of the above amino acid sequences. The antibody used in the present invention includes all antibodies that bind to these peptides and exhibit antitumor activity.

**[0023]** The antibody against CAPRIN-1 used in the present invention may be any type of antibody that can exert antitumor activity and includes, for example, monoclonal antibodies, polyclonal antibodies, recombinant antibodies, for example, synthetic antibodies, multispecific antibodies (e.g., diabody and triabody), humanized antibodies, chimeric antibodies, and single-chain antibodies (scFv), human antibodies, and their antibody fragments, for example, Fab, F(ab')<sub>2</sub>, and Fv. These antibodies and fragments thereof can be prepared by methods generally known to those skilled in the art. The antibody according to the present invention is desirably an antibody capable of specifically binding to the CAPRIN-1 protein and is preferably a monoclonal antibody. A polyclonal antibody may be used as long as homogeneous antibodies can be stably produced. In the case of a human subject, a human antibody or a humanized antibody is desirable for avoiding or suppressing rejection.

**[0024]** As used herein, the phrase "specifically binding to the CAPRIN-1 protein" means that the antibody specifically binds to the CAPRIN-1 protein without substantially binding to other proteins.

**[0025]** The antibody that can be used in the present invention can be examined for its antitumor activity, as described later, by examining *in vivo* the inhibition of tumor growth in a cancer-bearing animal or by examining *in vitro* the presence or absence of immunocyte- or complement-mediated cytotoxic activity exhibited by the antibody against tumor cells expressing the polypeptide.

**[0026]** The subject to receive the treatment of pancreatic cancer according to the present invention is a mammal such as a human, a pet animal, livestock, or a sport animal, preferably a human.

**[0027]** Hereinafter, antigen preparation, antibody preparation, and a pharmaceutical composition according to the present invention will be described.

#### <Preparation of antigen for antibody preparation>

**[0028]** Proteins or fragments thereof used as sensitizing antigens for obtaining the antibody against CAPRIN-1 used in the present invention are not limited by animal species serving as their origins, including humans, dogs, cattle, horses, mice, rats, and chickens. The proteins or the fragments thereof, however, are preferably selected in view of compatibility with parent cells for use in cell fusion. In general, mammal-derived proteins are preferred. Particularly, human-derived proteins are preferred. For example, when CAPRIN-1 is human CAPRIN-1, human CAPRIN-1 proteins, partial peptides thereof, or cells expressing human CAPRIN-1 can be used.

**[0029]** The nucleotide sequences and amino acid sequences of human CAPRIN-1 and homologs thereof can be obtained, for example, by accessing to GenBank (NCBI, USA) to use BLAST or FASTA algorithm (Karlin and Altschul, Proc. Natl. Acad. Sci. USA, 90: 5873-5877, 1993; and Altschul et al., Nucleic Acids Res. 25: 3389-3402, 1997).

**[0030]** In the present invention, with reference to the nucleotide sequence (SEQ ID NO: 1 or 3) or amino acid sequence (SEQ ID NO: 2 or 4) of human CAPRIN-1, targets are nucleic acids or proteins consisting of sequences having 70% to

100%, preferably 80% to 100%, more preferably 90% to 100%, further preferably 95% to 100%, for example, 97% to 100%, 98% to 100%, 99% to 100%, or 99.5% to 100% sequence identity to the nucleotide sequence or amino acid sequence of the ORF or mature portion of the reference. As used herein, the term "% sequence identity" means a percentage (%) of the number of identical amino acids (or bases) to the total number of amino acids (or bases) when two sequences are aligned such that the maximum degree of similarity or identity can be achieved with or without introduced gaps.

**[0031]** The fragments of each CAPRIN-1 protein have lengths ranging from the amino acid length of an epitope (or an antigenic determinant), which is the smallest unit recognized by the antibody, to less than the full-length of the protein. The epitope refers to a polypeptide fragment having antigenicity or immunogenicity in mammals, preferably humans. Its smallest unit consists of approximately 7 to 12 amino acid residues, for example, 8 to 11 amino acid residues. Specific examples thereof include an amino acid sequence represented by SEQ ID NO: 273, 266, 270, 272, or 269 and an amino acid sequence having 80% or higher, preferably 85% or higher, more preferably 90% or higher, further preferably 95% or higher, far more preferably 97 to 99% or higher sequence identity to the amino acid sequence.

**[0032]** Polypeptides comprising the above human CAPRIN-1 proteins and partial peptides thereof can be synthesized according to chemical synthesis methods, for example, Fmoc (fluorenylmethyloxycarbonyl) and tBoc (t-butyloxycarbonyl) methods (Seikagaku Jikken Koza (Biochemical Experimentation Course in English) 1, the Japanese Biochemical Society ed., Protein Chemistry IV, Chemical Modification and Peptide Synthesis, Tokyo Kagaku Dojin Co., Ltd. (Japan), 1981). Also, these polypeptides can be synthesized by routine methods using various commercially available peptide synthesizers. Alternatively, polynucleotides encoding the polypeptides may be prepared using genetic engineering approaches known in the art (Sambrook et al., Molecular Cloning, the 2nd edition, Current Protocols in Molecular Biology (1989), Cold Spring Harbor Laboratory Press; Ausubel et al., Short Protocols in Molecular Biology, the 3rd edition, A compendium of Methods from Current Protocols in Molecular Biology (1995), John Wiley & Sons; etc.) and incorporated into expression vectors, which are then introduced into host cells so that the host cells produce the polypeptides. In this way, the polypeptides of interest can be obtained.

**[0033]** The polynucleotides encoding the polypeptides can be readily prepared by genetic engineering approaches known in the art or routine methods using commercially available nucleic acid synthesizers. For example, a DNA comprising the nucleotide sequence of SEQ ID NO: 1 can be prepared by PCR using a human chromosomal DNA or cDNA library as a template and a pair of primers designed so as to be capable of amplifying the nucleotide sequence represented by SEQ ID NO: 1. Reaction conditions for this PCR can be appropriately determined. Examples of the conditions can include, but not limited to, 30 cycles each involving reaction steps consisting of 94°C for 30 seconds (denaturation), 55°C for 30 seconds to 1 minute (annealing), and 72°C for 2 minutes (elongation) using thermostable DNA polymerase (e.g., Taq polymerase) and a Mg<sup>2+</sup>-containing PCR buffer, followed by reaction at 72°C for 7 minutes. The PCR approach, conditions, etc. are described in, for example, Ausubel et al., Short Protocols in Molecular Biology, the 3rd edition, A Compendium of Methods from Current Protocols in Molecular Biology (1995), John Wiley & Sons (particularly, Chapter 15).

**[0034]** Also, appropriate probes or primers can be prepared on the basis of information about the nucleotide sequences and the amino acid sequences represented by SEQ ID NOs: 1 to 30 in the Sequence Listing described herein, and used in the screening of, for example, a human cDNA library, to isolate the desired DNA. Preferably, such a cDNA library is produced from cells, organs, or tissues expressing proteins shown in even-numbered SEQ ID NOs: 2 to 30. Examples of such cells or tissues include cells or tissues derived from the testis or from cancers or tumors such as leukemia, breast cancer, lymphoma, brain tumor, lung cancer, colorectal cancer, and pancreatic cancer. These manipulations, including the preparation of probes or primers, the construction of a cDNA library, the screening of the cDNA library, and the cloning of the gene of interest, are known to those skilled in the art and can be performed according to methods described in, for example, Sambrook et al., Molecular Cloning, the 2nd edition, Current Protocols in Molecular Biology (1989), and Ausubel et al. (ibid.). DNAs encoding the human CAPRIN-1 proteins and the partial peptides thereof can be obtained from the DNAs thus obtained.

**[0035]** The host cells may be any cell capable of expressing the above polypeptides. Examples of prokaryotic cells include, but not limited to, *E. coli*. Examples of eukaryotic cells include, but not limited to: mammalian cells such as monkey kidney cells COS1 and Chinese hamster ovary cells CHO; a human embryonic kidney cell line HEK293; mouse embryonic skin cell line NIH3T3; yeast cells such as budding yeast and fission yeast cells; silkworm cells; and *Xenopus* egg cells.

**[0036]** In the case of using prokaryotic cells as the host cells, the expression vectors used have an origin that permits replication in the prokaryotic cells, a promoter, a ribosomal binding site, a multicloning site, a terminator, a drug resistance gene, an auxotrophic complementary gene, etc. Examples of expression vectors for *E. coli* can include pUC series, pBluescript II, pET expression systems, and pGEX expression systems. The DNAs encoding the above polypeptides can be incorporated into such expression vectors, with which prokaryotic host cells are then transformed, followed by culture of the obtained transformants so that the polypeptides encoded by the DNAs are expressed in the prokaryotic host cells. In this respect, the polypeptides may be expressed as fusion proteins with other proteins.

**[0037]** In the case of using eukaryotic cells as the host cells, expression vectors for eukaryotic cells having a promoter, a splicing region, a poly(A) addition site, etc. are used as the expression vectors. Examples of such expression vectors can include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV, pRS, pcDNA3, and pYES2 vectors. In the same way as above, the DNAs encoding the above polypeptides can be incorporated into such expression vectors, with which eukaryotic host cells are then transformed, followed by culture of the obtained transformants so that the polypeptides encoded by the DNAs are expressed in the eukaryotic host cells. In the case of using expression vectors such as pIND/V5-His, pFLAG-CMV-2, pEGFP-N1, or pEGFP-C1, the polypeptides may be expressed as various fusion proteins tagged with His tag (e.g., (His)<sub>6</sub> to (His)<sub>10</sub>), FLAG tag, myc tag, HA tag, GFP, or the like.

**[0038]** The expression vectors can be introduced into the host cells using well known methods such as electroporation, a calcium phosphate method, a liposome method, a DEAE dextran method, microinjection, viral infection, lipofection, and binding with cell-penetrating peptides.

**[0039]** The polypeptide of interest can be isolated and purified from the host cells by a combination of separation procedures known in the art. Examples thereof include, but not limited to, treatment with a denaturant (e.g., urea) or a surfactant, ultrasonication, enzymatic digestion, salting-out, solvent fractionation and precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing electrophoresis, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, and reverse-phase chromatography.

#### <Structure of antibody>

**[0040]** Antibodies are usually heteromultimeric glycoproteins each comprising at least two heavy chains and two light chains. The antibodies, except for IgM, are heterotetrameric glycoproteins of approximately 150 kDa each composed of two identical light (L) chains and two identical heavy (H) chains. Typically, each light chain is connected to a heavy chain via a single covalent disulfide bond, though the number of disulfide bonds between heavy chains varies among different immunoglobulin isotypes. Each of the heavy and light chains also has an intrachain disulfide bond. Each heavy chain has a variable domain (VH region) at one end, followed by a series of constant regions. Each light chain has a variable domain (VL region) at one end and has a single constant region at the other end. The light chain constant region is aligned with the first heavy chain constant region, while the light chain variable domain is aligned with the heavy chain variable domain. Particular regions called complementarity determining regions (CDRs) in the antibody variable domains exhibit specific variability and impart binding specificity to the antibody. Portions relatively conserved in the variable regions are called framework regions (FRs). The complete heavy and light chain variable domains each comprise four FRs connected via three CDRs. These three CDRs are called CDRH1, CDRH2, and CDRH3 in this order from the N-terminus of the heavy chain. Likewise, the CDRs are called CDRL1, CDRL2, and CDRL3 in the light chain. CDRH3 is most important for the binding specificity of the antibody for its antigen. In addition, CDRs in each chain are kept close to each other by the FR regions and contribute to the formation of an antigen-binding site in the antibody, together with CDRs in the other chain. The constant regions do not directly contribute to antibody-antigen binding, but exhibit various effector functions, for example, involvement in antibody-dependent cellular cytotoxicity (ADCC), phagocytosis mediated by binding to an Fcγ receptor, half-life/clearance rate mediated by a neonatal Fc receptor (FcRn), and complement-dependent cytotoxicity (CDC) mediated by a C1q component in the complement cascade.

#### <Preparation of antibody>

**[0041]** The anti-CAPRIN-1 antibody according to the present invention means an antibody having immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof.

**[0042]** As used herein, the "immunological reactivity" means the property of the antibody binding to the CAPRIN-1 antigen *in vivo*. Via such binding, the antibody exerts the function of damaging (e.g., killing, suppressing, or regressing) tumor. Specifically, the antibody used in the present invention is not limited by its type as long as the antibody can damage pancreatic cancer as a result of binding to the CAPRIN-1 protein.

**[0043]** Examples of the antibody include monoclonal antibodies, polyclonal antibodies, synthetic antibodies, multispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies, single-chain antibodies, and antibody fragments (e.g., Fab, F(ab')<sub>2</sub>, and Fv). Also, the antibody is any class of immunoglobulin molecule, for example, IgG, IgE, IgM, IgA, IgD, or IgY, or any subclass, for example, IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub>, IgG<sub>4</sub>, IgA<sub>1</sub>, or IgA<sub>2</sub>.

**[0044]** The antibody may be further modified by acetylation, formylation, amidation, phosphorylation, PEGylation, or the like, in addition to glycosylation.

**[0045]** Hereinafter, preparation examples of various antibodies will be described.

**[0046]** When the antibody of the present invention is a monoclonal antibody, for example, CAPRIN-1 proteins, pancreatic cancer cells expressing CAPRIN-1, or a cell line thereof (e.g., Capan-2) is administered to each mouse for immunization. The spleen is extracted from this mouse. After separation of spleen cells, the cells are fused with mouse myeloma cells. Clones producing antibodies having a cancer cell growth inhibitory effect are selected from among the

obtained fusion cells (hybridomas). The hybridomas producing monoclonal antibodies having a cancer cell growth inhibitory effect are isolated and cultured. The antibody of interest can be prepared by purification from the culture supernatant according to a general affinity purification method.

**[0047]** The monoclonal antibody-producing hybridomas may be prepared, for example, as follows: first, animals are immunized with sensitizing antigens according to a method known in the art. This immunization method generally comprises intraperitoneally or subcutaneously injecting the sensitizing antigens to mammals. Specifically, the sensitizing antigens are diluted with or suspended in PBS (phosphate-buffered saline), physiological saline, or the like into an appropriate amount and then mixed, if desired, with an appropriate amount of a conventional adjuvant, for example, a complete Freund's adjuvant. After emulsification, the resulting emulsion is administered to each mammal several times every 4 to 21 days. Alternatively, an appropriate carrier may be used for the immunization with sensitizing antigens.

**[0048]** After confirmation of a rise in the level of the desired antibody in the serum of the mammal thus immunized, immunocytes are collected from the mammal and subjected to cell fusion. Preferred examples of the immunocytes particularly include spleen cells.

**[0049]** Mammalian myeloma cells are used as partner parent cells to be fused with the immunocytes. Various cell lines known in the art, for example, P3U1 (P3-X63Ag8U1), P3 (P3x63Ag8.653) (J. Immunol. (1979) 123, 1548-1550), P3x63Ag8U.1 (Current Topics in Microbiology and Immunology (1978) 81, 1-7), NS-1 (Kohler, G. and Milstein, C. Eur. J. Immunol. (1976) 6, 511-519), MPC-11 (Margulies, D.H. et al., Cell (1976) 8, 405-415), SP2/0 (Shulman, M. et al., Nature (1978) 276, 269-270), FO (deSt. Groth, S.F. et al., J. Immunol. Methods (1980) 35, 1-21), S194 (Trowbridge, I.S. J. Exp. Med. (1978) 148, 313-323), and R210 (Galfre, G. et al., Nature (1979) 277, 131-133), are preferably used as the myeloma cells.

**[0050]** The cell fusion between the immunocytes and the myeloma cells can be performed basically according to a method known in the art, for example, the method of Kohler and Milstein (Kohler, G. and Milstein, C. Methods Enzymol. (1981) 73, 3-46).

**[0051]** More specifically, the cell fusion is carried out, for example, in the presence of a cell fusion promoter in a conventional nutrient medium. For example, polyethylene glycol (PEG) or Sendai virus (hemagglutinating virus of Japan (HVJ)) is used as the fusion promoter. If desired, an auxiliary such as dimethyl sulfoxide may be further added in order to enhance fusion efficiency.

**[0052]** The ratio between the immunocytes and the myeloma cells used can be arbitrarily set. For example, the amount of the immunocytes is preferably set to 1 to 10 times the amount of the myeloma cells. Examples of the medium that can be used in the cell fusion include RPMI1640 and MEM media suitable for the growth of the myeloma cell lines as well as conventional media for use in this type of cell culture. In addition, a serum supplement such as fetal calf serum (FCS) may be used in combination with these cells.

**[0053]** For the cell fusion, the immunocytes and the myeloma cells are well mixed in a predetermined amount of the medium. A PEG solution (average molecular weight: for example, approximately 1000 to 6000) preheated to approximately 37°C is usually added to the mixture at a concentration of 30 to 60% (w/v) and mixed therewith to form the hybridomas of interest. Subsequently, procedures of sequentially adding an appropriate medium and removing the supernatant by centrifugation are repeated to remove cell fusion agents or the like unfavorable for the growth of the hybridomas.

**[0054]** The hybridomas thus obtained are cultured in a conventional selective medium, for example, a HAT medium (a medium containing hypoxanthine, aminopterin, and thymidine) for selection. Culture in the HAT medium is continued for a period (usually, several days to several weeks) sufficient for the death of cells (non-fused cells) other than the hybridomas of interest. Subsequently, hybridomas producing the antibody of interest are screened for and cloned as single clones by a conventional limiting dilution method.

**[0055]** In addition to such obtainment of the hybridomas by the immunization of non-human animals with antigens, hybridomas producing human antibodies having the desired activity (e.g., cell growth inhibitory activity) may be obtained by sensitizing human lymphocytes, for example, EB virus-infected human lymphocytes, with proteins, protein-expressing cells, or lysates thereof *in vitro* and fusing the sensitized lymphocytes with human-derived myeloma cells capable of dividing permanently, for example, U266 (Accession No. TIB 196).

**[0056]** The monoclonal antibody-producing hybridomas thus prepared can be subcultured in a conventional medium and can also be stored for a long period in liquid nitrogen.

**[0057]** Specifically, the desired antigens or cells expressing the desired antigens are used as sensitizing antigens in immunization according to a conventional immunization method. The obtained immunocytes are fused with parent cells known in the art according to a conventional cell fusion method. Monoclonal antibody-producing cells (hybridomas) can be screened for by a conventional screening method to prepare the antibody of interest.

**[0058]** Another example of the antibody that may be used in the present invention is a polyclonal antibody. The polyclonal antibody can be obtained, for example, as follows:

**[0059]** Serum is obtained from small animals such as mice, human antibody-producing mice, or rabbits immunized with natural CAPRIN-1 proteins or recombinant CAPRIN-1 proteins expressed as fusion proteins with GST or the like

in microorganisms such as *E. coli*, or partial peptides thereof. This serum is purified using, for example, ammonium sulfate precipitation, protein A or protein G columns, DEAE ion-exchange chromatography, or affinity columns coupled with CAPRIN-1 proteins or synthetic peptides to prepare the polyclonal antibody of interest. In Examples described later, rabbit polyclonal antibodies against CAPRIN-1 proteins were prepared and confirmed to have an antitumor effect.

**[0060]** In this context, for example, KM mice (Kirin Pharma Co., Ltd./Medarex) and Xeno mice (Amgen Inc.) are known as the human antibody-producing mice (e.g., International Publication Nos. WO02/43478 and WO02/092812). Complete human polyclonal antibodies can be obtained from the blood of such mice immunized with CAPRIN-1 proteins or fragments thereof. Alternatively, spleen cells may be isolated from the mice thus immunized and fused with myeloma cells. In this way, human monoclonal antibodies can be obtained.

**[0061]** The antigens can be prepared according to, for example, a method using animal cells (JP Patent Publication (Kohyo) No. 2007-530068 A (2007)) or a method using baculovirus (e.g., International Publication No. WO98/46777). Antigens having low immunogenicity may be bound to immunogenic macromolecules such as albumin for immunization.

**[0062]** Alternatively, recombinant antibodies may be used, which are produced using a gene recombination technique which comprises: cloning antibody genes from hybridomas; incorporating the antibody genes into appropriate vectors; and introducing the vectors into hosts (see, e.g., Carl, A.K. Borrebaeck, James, W. Larrick, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990). Specifically, antibody variable region (V region) cDNAs are synthesized from the mRNAs of hybridomas using reverse transcriptase. After obtainment of DNAs encoding the antibody V regions of interest, the DNAs are ligated with DNAs encoding the desired antibody constant regions (C regions). The resulting ligation products are incorporated into expression vectors. Alternatively, the antibody V region-encoding DNAs may be incorporated into expression vectors containing antibody C region DNAs. These DNAs are incorporated into the expression vectors so as to be expressed under the control of expression control regions, for example, an enhancer and a promoter. Next, host cells can be transformed with the resulting expression vectors and allowed to express antibodies.

**[0063]** The anti-CAPRIN-1 antibody used in the present invention is preferably a monoclonal antibody. Alternatively, the anti-CAPRIN-1 antibody of the present invention may be a polyclonal antibody, a genetically engineered antibody (chimeric antibody, humanized antibody, etc.), or the like.

**[0064]** The monoclonal antibody includes human monoclonal antibodies, non-human animal monoclonal antibodies (e.g., mouse, rat, rabbit, and chicken monoclonal antibodies), and the like. The monoclonal antibody may be prepared by the culture of hybridomas obtained by the fusion between spleen cells from non-human mammals (e.g., mice or human antibody-producing mice) immunized with CAPRIN-1 proteins and myeloma cells. In Examples described later, monoclonal antibodies were prepared and confirmed to have an antitumor effect on pancreatic cancer. These monoclonal antibodies each comprise a heavy chain variable (VH) region having an amino acid sequence of SEQ ID NO: 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 135, 145, 160, 170, 200, 210, 220, 230, 240, or 250 and a light chain variable (VL) region having an amino acid sequence of SEQ ID NO: 44, 54, 64, 74, 84, 94, 104, 114, 124, 139, 149, 155, 164, 174, 180, 185, 190, 195, 204, 214, 224, 234, 244, or 254, wherein the VH region comprises CDR1 represented by an amino acid sequence of SEQ ID NO: 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 132, 142, 157, 167, 197, 207, 217, 227, 237, or 247, CDR2 represented by an amino acid sequence of SEQ ID NO: 38, 48, 58, 68, 78, 88, 98, 108, 118, 128, 133, 143, 158, 168, 198, 208, 218, 228, 238, or 248, and CDR3 represented by an amino acid sequence of SEQ ID NO: 39, 49, 59, 69, 79, 89, 99, 109, 119, 129, 134, 144, 159, 169, 199, 209, 219, 229, 239, or 249, and the VL region comprises CDR1 represented by an amino acid sequence of SEQ ID NO: 41, 51, 61, 71, 81, 91, 101, 111, 121, 136, 146, 152, 161, 171, 177, 182, 187, 192, 201, 211, 221, 231, 241, or 251, CDR2 represented by an amino acid sequence of SEQ ID NO: 42, 52, 62, 72, 82, 92, 102, 112, 122, 137, 147, 153, 162, 172, 178, 183, 188, 193, 202, 212, 222, 232, 242, or 252, and CDR3 represented by an amino acid sequence of SEQ ID NO: 43, 53, 63, 73, 83, 93, 103, 113, 123, 138, 148, 154, 163, 173, 179, 184, 189, 194, 203, 213, 223, 233, 243, or 253.

**[0065]** The chimeric antibody is an antibody prepared from a combination of sequences derived from different animals and is, for example, an antibody composed of mouse antibody heavy and light chain variable regions and human antibody heavy and light chain constant regions. The chimeric antibody can be prepared using a method known in the art which involves, for example: ligating DNAs encoding antibody V regions with DNAs encoding human antibody C regions; incorporating the resulting ligation products into expression vectors; and introducing the vectors into hosts so that antibodies are produced.

**[0066]** The polyclonal antibody includes antibodies obtained from human antibody-producing animals (e.g., mice) immunized with CAPRIN-1 proteins.

**[0067]** The humanized antibody, also called reshaped human antibody, is an engineered antibody. The humanized antibody is constructed by grafting antibody CDRs derived from an immunized animal into human antibody complementarity determining regions of a human antibody. A general gene recombination approach therefor is also known.

**[0068]** Specifically, DNA sequences designed so as to link mouse antibody CDRs and human antibody framework regions (FRs) are synthesized by PCR using several prepared oligonucleotides having terminal portions overlapping with each other. The obtained DNAs are ligated with DNAs encoding human antibody constant regions. Subsequently,

the resulting ligation products are incorporated into expression vectors, which are then introduced into hosts for antibody production to obtain the antibody of interest (see European Patent Application Publication No. EP239400 and International Publication No. WO96/02576). The human antibody FRs connected via CDRs are selected such that the complementarity determining regions form a favorable antigen-binding site. If necessary, amino acids in the framework regions of antibody variable regions may be substituted such that the complementarity determining regions of the resulting reshaped human antibody form an appropriate antigen-binding site (Sato K. et al., Cancer Research 1993, 53: 851-856). In addition, these framework regions may be replaced with framework regions derived from various human antibodies (see International Publication No. WO99/51743).

**[0069]** The human antibody framework regions connected via CDRs are selected such that the complementarity determining regions form a favorable antigen-binding site. If necessary, amino acids in the framework regions of antibody variable regions may be substituted such that the complementarity determining regions of the resulting reshaped human antibody form an appropriate antigen-binding site (Sato K. et al., Cancer Research 1993, 53: 851-856).

**[0070]** Amino acids in variable regions (e.g., FRs) or constant regions of the chimeric antibody or the humanized antibody thus prepared may be substituted, for example, by other amino acids.

**[0071]** The amino acid substitution is the substitution of, for example, less than 15, less than 10, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less amino acids, preferably 1 to 5 amino acids, more preferably 1 or 2 amino acids. The substituted antibody should be functionally equivalent to an unsubstituted antibody. The substitution is desirably conservative amino acid substitution, which is the substitution between amino acids similar in properties such as charge, side chains, polarity, and aromaticity. The amino acids can be classified in terms of similar properties into, for example: basic amino acids (arginine, lysine, and histidine); acidic amino acids (aspartic acid and glutamic acid); uncharged polar amino acids (glycine, asparagine, glutamine, serine, threonine, cysteine, and tyrosine); nonpolar amino acids (leucine, isoleucine, alanine, valine, proline, phenylalanine, tryptophan, and methionine); branched amino acids (threonine, valine, and isoleucine); and aromatic amino acids (phenylalanine, tyrosine, tryptophan, and histidine).

**[0072]** Examples of modified antibodies can include antibodies bound with various molecules such as polyethylene glycol (PEG). In the modified antibody used in the present invention, the substance to be bound is not limited. In order to obtain such a modified antibody, the obtained antibody can be chemically modified. A method therefor has already been established in the art.

**[0073]** In this context, the phrase "functionally equivalent" means that an antibody concerned has biological or biochemical activity similar to that of the antibody used in the present invention, specifically, the antibody concerned has the function of damaging tumor and essentially causes no rejection when applied to humans, for example. Examples of such activity can include cell growth inhibitory activity and binding activity.

**[0074]** A method for preparing a polypeptide functionally equivalent to a certain polypeptide, which comprises introducing a mutation into a polypeptide, is well known to those skilled in the art. For example, those skilled in the art can appropriately introduce a mutation into the antibody used in the present invention using site-directed mutagenesis (Hashimoto-Gotoh, T. et al., (1995) Gene 152, 271-275; Zoller, MJ., and Smith, M. (1983) Methods Enzymol. 100, 468-500; Kramer, W. et al., (1984) Nucleic Acids Res. 12, 9441-9456; Kramer, W. and Fritz, HJ., (1987) Methods Enzymol. 154, 350-367; Kunkel, TA., (1985) Proc. Natl. Acad. Sci. USA. 82, 488-492; and Kunkel (1988) Methods Enzymol. 85, 2763-2766) or the like, thereby prepare an antibody functionally equivalent to the antibody of the present invention.

**[0075]** An antibody that recognizes an epitope of a CAPRIN-1 protein recognized by each anti-CAPRIN-1 antibody described above can be obtained by a method generally known to those skilled in the art. For example, the antibody can be obtained by a method which comprises determining the epitope of the CAPRIN-1 protein recognized by the anti-CAPRIN-1 antibody by a conventional method (e.g., epitope mapping) and preparing an antibody using a polypeptide having an amino acid sequence contained in the epitope as an immunogen, or a method which involves determining an epitope for an antibody prepared by a conventional method and selecting an antibody that recognizes the same epitope as that for the anti-CAPRIN-1 antibody. As used herein, the "epitope" refers to a polypeptide fragment having antigenicity or immunogenicity in mammals, preferably humans. Its smallest unit consists of approximately 7 to 12 amino acids, preferably 8 to 11 amino acids.

**[0076]** The antibody used in the present invention has an affinity constant  $K_a$  (kon/koff) of preferably at least  $10^7 \text{ M}^{-1}$ , at least  $10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$  at least  $5 \times 10^{10} \text{ M}^{-1}$  at least  $10^{11} \text{ M}^{-1}$  at least  $5 \times 10^{11} \text{ M}^{-1}$  at least  $10^{12} \text{ M}^{-1}$ , or at least  $10^{13} \text{ M}^{-1}$ .

**[0077]** The antibody used in the present invention can be conjugated with an antitumor agent. The conjugation of the antibody with the antitumor agent can be performed via a spacer having a group (e.g., a succinimidyl group, a formyl group, a 2-pyridyldithio group, a maleimidyl group, an alkoxycarbonyl group, or a hydroxy group) reactive with an amino group, a carboxyl group, a hydroxy group, a thiol group, or the like.

**[0078]** Examples of the antitumor agent include the following antitumor agents publicly known in literatures, etc.: paclitaxel, doxorubicin, daunorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephospho-

ramide, triethylenethiophosphoramide, trimethylolmelamine, bullatacin, bullatacinone, camptothecin, bryostatin, cal-  
 lystatin, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, eleutherobin, pancratistatin, sarcodictyin, spongistatin,  
 chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide  
 hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chloro-  
 zotocin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, dynemicin, clodronate, esperamicin, aclacino-  
 mycin, actinomycin, authramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromo-  
 mycin, dactinomycin, detorbicin, 6-diazo-5-oxo-L-norleucine, Adriamycin, epirubicin, esorubicin, idarubicin, marcellomy-  
 cin, mitomycin C, mycophenolic acid, nogalamycin, olivomycin, peplomycin, potfiromycin, puromycin, quelamycin, ro-  
 dorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate,  
 fludarabine, 6-mercaptapurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine,  
 dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens (e.g., calusterone, dromostanolone propionate, epitio-  
 stanol, mepitiostane, and testolactone), aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone, aldophos-  
 phamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, demecol-  
 cine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, lentinan, lonidamine, maytansine, ansamitocin,  
 mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic  
 acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, schizophyllan, spirogermanium, tenuazonic acid, triaziquone,  
 roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine,  
 docetaxel, chlorambucil, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, oxaliplatin, carboplatin, vinblastine,  
 etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatraxate, daunomycin, aminop-  
 terin, Xeloda, ibandronate, irinotecan, topoisomerase inhibitors, difluoromethylornithine (DMFO), retinoic acid, capecit-  
 abine, and pharmaceutically acceptable salts (known in the art) and derivatives (known in the art) thereof.

**[0079]** Alternatively, the antibody used in the present invention can be administered in combination with an antitumor  
 agent to produce a higher therapeutic effect. This approach is adaptable to a patient with cancer expressing CAPRIN-  
 1 either before or after surgical operation. This approach can be applied, particularly after surgery, to CAPRIN-1-ex-  
 pressing cancer, which has been treated conventionally with an antitumor agent alone, to produce higher prevention of  
 cancer recurrence or prolongation of survival time.

**[0080]** Examples of the antitumor agent used in the combined administration include the following antitumor agents  
 publicly known in literatures, etc.: paclitaxel, doxorubicin, daunorubicin, cyclophosphamide, methotrexate, 5-fluorouracil,  
 thiotepe, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylen-  
 emelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolmelamine, bullatacin, bullatacinone,  
 camptothecin, bryostatin, calystatin, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, eleutherobin, pancratista-  
 tin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlo-  
 rethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide,  
 uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, dynemicin,  
 clodronate, esperamicin, aclacinomycin, actinomycin, authramycin, azaserine, bleomycin, cactinomycin, carabycin, car-  
 minomycin, carzinophilin, chromomycin, dactinomycin, detorbicin, 6-diazo-5-oxo-L-norleucine, Adriamycin, epirubicin,  
 esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycin, peplomycin, potfiro-  
 mycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, de-  
 nopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptapurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-  
 azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, calusterone, dromostanolone  
 propionate, epitio stanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone,  
 aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestabucil, bisantrene, edatraxate, defofamine,  
 demecolcine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, lentinan, lonidamine, maytansine,  
 ansamitocin, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, po-  
 dophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, schizophyllan, spirogermanium, tenuazonic acid,  
 triaziquone, roridin A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman,  
 gacytosine, docetaxel, chlorambucil, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, oxaliplatin, carboplatin, vin-  
 blastine, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatraxate, daunomycin,  
 aminopterin, Xeloda, ibandronate, irinotecan, topoisomerase inhibitors, difluoromethylornithine (DMFO), retinoic acid,  
 capecitabine, and pharmaceutically acceptable salts (known in the art) and derivatives (known in the art) thereof. Of  
 these antitumor agents, cyclophosphamide, paclitaxel, docetaxel, vinorelbine, or the like is particularly preferably used.

**[0081]** Alternatively, the antibody used in the present invention may be bound to a radioisotope publicly known in  
 literatures, etc., such as  $^{211}\text{At}$ ,  $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{90}\text{Y}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{153}\text{Sm}$ ,  $^{212}\text{Bi}$ ,  $^{32}\text{P}$ ,  $^{175}\text{Lu}$ , or  $^{176}\text{Lu}$ . Desirably, a radioisotope  
 effective for the treatment or diagnosis of tumor is used.

**[0082]** The antibody used in the present invention is an antibody having immunological reactivity with CAPRIN-1 or  
 an antibody specifically binding to CAPRIN-1 and exhibits cytotoxic activity or tumor growth inhibitory effect on pancreatic  
 cancer. The antibody should have a structure that causes little or no rejection in recipient animals. Examples of such  
 antibodies include human antibodies, humanized antibodies, chimeric antibodies (e.g., human-mouse chimeric antibod-

ies), single-chain antibodies, and multispecific antibodies (e.g., diabody and triabody) when the recipient animals are humans. These antibodies have heavy and light chain variable regions derived from a human antibody or have heavy and light chain variable regions with complementarity determining regions (CDR1, CDR2, and CDR3) derived from a non-human animal antibody and framework regions derived from a human antibody. Alternatively, these antibodies are recombinant antibodies having heavy and light chain variable regions derived from a non-human animal antibody and heavy and light chain constant regions derived from a human antibody. The antibody of the present invention is preferably the former two antibodies.

**[0083]** Such recombinant antibodies can be prepared as follows: DNAs encoding monoclonal antibodies (e.g., human, mouse, rat, rabbit, and chicken monoclonal antibodies) against human CAPRIN-1 are cloned from antibody-producing cells such as hybridomas and used as templates in RT-PCR or the like to prepare DNAs encoding the light and heavy chain variable regions of the antibodies. The respective sequences of the light and heavy chain variable regions and the respective sequences of CDR1, CDR2, and CDR3 in each region are determined on the basis of the Kabat EU numbering system (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institute of Health, Bethesda, Md. (1991)).

**[0084]** Such a DNA encoding each variable region or a DNA encoding each CDR is prepared using a gene recombination technique (Sambrook et al., Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory Press (1989)) or a DNA synthesizer. In this context, the human monoclonal antibody-producing hybridomas can be prepared by immunizing human antibody-producing animals (e.g., mice) with human CAPRIN-1 and then fusing spleen cells excised from the immunized animals with myeloma cells. Aside from this, DNAs encoding human antibody-derived light or heavy chain variable and constant regions are prepared, if necessary, using a gene recombination technique or a DNA synthesizer.

**[0085]** For the humanized antibody, DNAs in which the CDR coding sequences in DNAs encoding a human antibody-derived light or heavy chain variable regions are substituted by corresponding CDR coding sequences of a non-human animal (e.g., mouse, rat, or chicken)-derived antibody can be prepared and ligated with the DNAs encoding human antibody-derived light or heavy chain constant regions to prepare a DNA encoding the humanized antibody.

**[0086]** For the chimeric antibody, DNAs encoding light or heavy chain variable regions of a non-human animal (e.g., mouse, rat, or chicken)-derived antibody can be ligated with DNAs encoding human antibody-derived light or heavy chain constant regions to prepare a DNA encoding the chimeric antibody.

**[0087]** The single-chain antibody refers to an antibody comprising heavy and light chain variable regions linearly linked to each other via a linker. A DNA encoding the single-chain antibody can be prepared by ligating a DNA encoding the heavy chain variable region, a DNA encoding the linker, and a DNA encoding the light chain variable region. In this context, the heavy and light chain variable regions are both derived from a human antibody or derived from a human antibody having CDRs substituted by CDRs of a non-human animal (e.g., mouse, rat, or chicken)-derived antibody. The linker consists of 12 to 19 amino acids. Examples thereof include (G<sub>4</sub>S)<sub>3</sub> consisting of 15 amino acids (G.B. Kim et al., Protein Engineering Design and Selection 2007, 20 (9): 425-432).

**[0088]** The bispecific antibody (diabody) refers to an antibody capable of specifically binding to two different epitopes. A DNA encoding the bispecific antibody can be prepared by ligating, for example, a DNA encoding a heavy chain variable region A, a DNA encoding a light chain variable region B, a DNA encoding a heavy chain variable region B, and a DNA encoding a light chain variable region A in this order (provided that the DNA encoding a light chain variable region B and the DNA encoding a heavy chain variable region B are ligated via a DNA encoding a linker as described above). In this context, the heavy and light chain variable regions are all derived from a human antibody or derived from a human antibody having CDRs substituted by CDRs of a non-human animal (e.g., mouse, rat, or chicken)-derived antibody.

**[0089]** The recombinant DNAs thus prepared can be incorporated into one or more appropriate vectors, which are then introduced into host cells (e.g., mammalian cells, yeast cells, and insect cells) so that the DNAs are (co)expressed to produce recombinant antibodies (P.J. Delves., ANTIBODY PRODUCTION ESSENTIAL TECHNIQUES., 1997 WILEY, P. Shepherd and C. Dean., Monoclonal Antibodies., 2000 OXFORD UNIVERSITY PRESS; and J.W. Goding., Monoclonal Antibodies: principles and practice., 1993 ACADEMIC PRESS).

**[0090]** Examples of the antibody of the present invention prepared by any of the methods described above include the following antibodies (a) to (y):

(a) an antibody comprising a heavy chain variable region comprising complementarity determining regions (CDRs) of SEQ ID NOs: 37, 38, and 39 and a light chain variable region comprising CDRs of SEQ ID NOs: 41, 42, and 43 (e.g., an antibody comprising a heavy chain variable region of SEQ ID NO: 40 and a light chain variable region of SEQ ID NO: 44);

(b) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 47, 48, and 49 and a light chain variable region comprising CDRs of SEQ ID NOs: 51, 52, and 53 (e.g., an antibody comprising a heavy chain variable region of SEQ ID NO: 50 and a light chain variable region of SEQ ID NO: 54);

(c) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 57, 58, and 59 and a



heavy chain variable region of SEQ ID NO: 220 and a light chain variable region of SEQ ID NO: 224);

(w) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 227, 228, and 229 and a light chain variable region comprising CDRs of SEQ ID NOs: 231, 232, and 233 (e.g., an antibody comprising a heavy chain variable region of SEQ ID NO: 230 and a light chain variable region of SEQ ID NO: 234);

(x) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 237, 238, and 239 and a light chain variable region comprising CDRs of SEQ ID NOs: 241, 242, and 243 (e.g., an antibody comprising a heavy chain variable region of SEQ ID NO: 240 and a light chain variable region of SEQ ID NO: 244);

(y) an antibody comprising a heavy chain variable region comprising CDRs of SEQ ID NOs: 247, 248, and 249 and a light chain variable region comprising CDRs of SEQ ID NOs: 251, 252, and 253 (e.g., an antibody comprising a heavy chain variable region of SEQ ID NO: 250 and a light chain variable region of SEQ ID NO: 254).

**[0091]** In this context, the amino acid sequences represented by SEQ ID NOs: 67, 68, and 69, SEQ ID NOs: 77, 78, and 79, SEQ ID NOs: 87, 88, and 89, SEQ ID NOs: 97, 98, and 99, SEQ ID NOs: 107, 108, and 109, SEQ ID NOs: 117, 118, and 119, SEQ ID NOs: 127, 128, and 129, SEQ ID NOs: 132, 133, and 134, SEQ ID NOs: 142, 143, and 144, SEQ ID NOs: 157, 158, and 159, SEQ ID NOs: 167, 168, and 169, SEQ ID NOs: 167, 168, and 169, SEQ ID NOs: 197, 198, and 199, SEQ ID NOs: 207, 208, and 209, SEQ ID NOs: 217, 218, and 219, SEQ ID NOs: 227, 228, and 229, SEQ ID NOs: 237, 238, and 239, SEQ ID NOs: 247, 248, and 249 correspond to CDR1, CDR2, and CDR3, respectively, of a mouse antibody heavy chain variable region. The amino acid sequences represented by SEQ ID NOs: 71, 72, and 73, SEQ ID NOs: 81, 82, and 83, SEQ ID NOs: 91, 92, and 93, SEQ ID NOs: 101, 102, and 103, SEQ ID NOs: 111, 112, and 113, SEQ ID NOs: 121, 122, and 123, SEQ ID NOs: 136, 137, and 138, SEQ ID NOs: 146, 147, and 148, SEQ ID NOs: 152, 153, and 154, SEQ ID NOs: 161, 162, and 163, SEQ ID NOs: 171, 172, and 173, SEQ ID NOs: 177, 178, and 179, SEQ ID NOs: 182, 183, and 184, SEQ ID NOs: 187, 188, and 189, SEQ ID NOs: 192, 193, and 194, SEQ ID NOs: 201, 202, and 203, SEQ ID NOs: 211, 212, and 213, SEQ ID NOs: 221, 222, and 223, SEQ ID NOs: 231, 232, and 233, SEQ ID NOs: 241, 242, and 243, SEQ ID NOs: 251, 252 and 253 correspond to CDR1, CDR2, and CDR3, respectively, of a mouse antibody light chain variable region.

**[0092]** Also, the amino acid sequences represented by SEQ ID NOs: 37, 38, and 39, SEQ ID NOs: 47, 48, and 49, or SEQ ID NOs: 57, 58, and 59 correspond to CDR1, CDR2, and CDR3, respectively, of a chicken antibody heavy chain variable region. The amino acid sequences represented by SEQ ID NOs: 41, 42, and 43, SEQ ID NOs: 51, 52, and 53, or SEQ ID NOs: 61, 62, and 63 correspond to CDR1, CDR2, and CDR3, respectively, of a chicken antibody light chain variable region.

**[0093]** Examples of the humanized antibody, the chimeric antibody, the single-chain antibody, or the multispecific antibody used in the present invention include the following antibodies, wherein the antibody (a) above is used as an example:

(i) an antibody comprising a heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 37, 38, and 39 and the amino acid sequences of human antibody-derived framework regions and a light chain variable region comprising the amino acid sequences of SEQ ID NOs: 41, 42, and 43 and the amino acid sequences of human antibody-derived framework regions;

(ii) an antibody comprising a heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 37, 38, and 39 and the amino acid sequences of human antibody-derived framework regions, a heavy chain constant region comprising a human antibody-derived amino acid sequence, a light chain variable region comprising the amino acid sequences of SEQ ID NOs: 41, 42, and 43 and the amino acid sequences of human antibody-derived framework regions, and a light chain constant region comprising a human antibody-derived amino acid sequence; and

(iii) an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 40, a heavy chain constant region comprising a human antibody-derived amino acid sequence, a light chain variable region comprising the amino acid sequence of SEQ ID NO: 44, and a light chain constant region comprising a human antibody-derived amino acid sequence.

**[0094]** The sequences of the constant and variable regions of human antibody heavy and light chains are available from, for example, NCBI (USA; GenBank, UniGene, etc.). For example, the following sequences can be referred to: Accession No. J00228 for a human IgG<sub>1</sub> heavy chain constant region; Accession No. J00230 for a human IgG<sub>2</sub> heavy chain constant region; Accession No. X03604 for a human IgG<sub>3</sub> heavy chain constant region; Accession No. K01316 for a human IgG<sub>4</sub> heavy chain constant region; Accession Nos. V00557, X64135, and X64133 for a human light chain  $\kappa$  constant region; and Accession Nos. X64132 and X64134 for a human light chain  $\lambda$  constant region.

**[0095]** Preferably, these antibodies have cytotoxic activity and can thereby exert an antitumor effect.

**[0096]** The above particular sequences of the heavy and light chain variable regions and CDRs in each antibody are provided merely for illustrative purposes. The antibody of the present invention should not be limited by the particular sequences. Hybridomas capable of producing anti-human CAPRIN-1 human antibodies or non-human animal antibodies

(e.g., mouse antibodies) different from those described above are prepared, and monoclonal antibodies produced by the hybridomas are recovered and assessed as being (or being not) the antibodies of interest with immunological binding activity against human CAPRIN-1 and cytotoxic activity as indicators. The monoclonal antibody-producing hybridomas of interest are thereby identified. Then, DNAs encoding heavy and light chain variable regions of the antibodies of interest are produced from the hybridomas and sequenced, as described above. The DNAs are used for the preparation of the different antibodies.

**[0097]** The antibody used in the present invention may be any of the antibodies (i) to (iii), etc. having a substitution(s), deletion(s), or addition(s) of one or several (preferably 1 or 2) amino acids, particularly in a framework region sequence and/or a constant region sequence, as long as the antibody has such specificity that it can specifically recognize CAPRIN-1. In this context, the term "several" means 2 to 5, preferably 2 or 3.

**[0098]** The antitumor effect of the anti-CAPRIN-1 antibody used in the present invention on CAPRIN-1-expressing pancreatic cancer cells seems to be brought about by the following mechanism: effector cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) against the CAPRIN-1-expressing cells.

**[0099]** Thus, the anti-CAPRIN-1 antibody used in the present invention can be evaluated for its activity by determining *in vitro* the ADCC activity or the CDC activity against CAPRIN-1-expressing pancreatic cancer cells as specifically shown below in Examples.

**[0100]** The anti-CAPRIN-1 antibody used in the present invention binds to CAPRIN-1 proteins on pancreatic cancer cells and exhibits an antitumor effect through the above activity. Thus, the anti-CAPRIN-1 antibody of the present invention is presumably useful in the treatment of pancreatic cancer. Specifically, the present invention provides a pharmaceutical composition for treatment of pancreatic cancer, comprising the anti-CAPRIN-1 antibody as an active ingredient. The anti-CAPRIN-1 antibody used for the purpose of administration to human bodies (antibody therapy) is preferably a human antibody or a humanized antibody for reducing immunogenicity.

**[0101]** The anti-CAPRIN-1 antibody with higher binding affinity for a CAPRIN-1 protein on pancreatic cancer cell surface exerts stronger antitumor activity. Thus, a stronger antitumor effect can be expected if an anti-CAPRIN-1 antibody having high binding affinity for the CAPRIN-1 protein can be obtained. Such an antibody is adaptable to a pharmaceutical composition intended for the treatment of pancreatic cancer. Desirably, such high binding affinity is preferably at least  $10^7 \text{ M}^{-1}$ , at least  $10^8 \text{ M}^{-1}$ , at least  $5 \times 10^8 \text{ M}^{-1}$ , at least  $10^9 \text{ M}^{-1}$ , at least  $5 \times 10^9 \text{ M}^{-1}$ , at least  $10^{10} \text{ M}^{-1}$ , at least  $5 \times 10^{10} \text{ M}^{-1}$ , at least  $10^{11} \text{ M}^{-1}$ , at least  $5 \times 10^{11} \text{ M}^{-1}$ , at least  $10^{12} \text{ M}^{-1}$ , or at least  $10^{13} \text{ M}^{-1}$ , in terms of an association constant (affinity constant)  $K_a$  ( $k_{on}/k_{off}$ ), as described above.

<Binding to antigen-expressing cells>

**[0102]** The ability of the antibody to bind to CAPRIN-1 can be determined by use of binding assay using, for example, ELISA, Western blot, immunofluorescence, and flow cytometry analysis, as described in Examples.

<Immunohistochemical staining>

**[0103]** The antibody that recognizes CAPRIN-1 can be tested for its reactivity with CAPRIN-1 by an immunohistochemical method well known to those skilled in the art using a paraformaldehyde- or acetone-fixed frozen section or paraformaldehyde-fixed paraffin-embedded section of a tissue obtained from a patient during surgical operation or from an animal carrying a xenograft tissue inoculated with a cell line expressing CAPRIN-1 either spontaneously or after transfection.

**[0104]** For immunohistochemical staining, the antibody reactive with CAPRIN-1 can be stained by various methods. For example, the antibody can be visualized through reaction with a horseradish peroxidase-conjugated goat anti-mouse antibody or goat anti-rabbit antibody.

<Pharmaceutical composition>

**[0105]** A target of the pharmaceutical composition for treatment and/or prevention of pancreatic cancer of the present invention is not particularly limited as long as the target is pancreatic cancer (cells) expressing a CAPRIN-1 gene.

**[0106]** The terms "tumor" and "cancer" used herein mean malignant neoplasm and are used interchangeably with each other.

**[0107]** Pancreatic cancer targeted in the present invention is pancreatic cancer expressing a gene encoding a polypeptide comprising an amino acid sequence of any of even-numbered SEQ ID NOs: 2 to 30 or a partial sequence thereof consisting of 7 to 12 or more consecutive amino acids.

**[0108]** Examples of the pancreatic cancer include, but not limited to, pancreatic ductal carcinoma, invasive pancreatic ductal carcinoma, pancreatic adenocarcinoma, acinar cell carcinoma, adenosquamous carcinoma, giant cell tumor,

intraductal papillary-mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), pancreatoblastoma, serous cystadenocarcinoma, solid-pseudopapillary tumor (SPT), gastrinomas (Zollinger-Ellison syndrome), glucagonomas, insulinoma, multiple endocrine neoplasia type-1 (MEN1) (Wermer's syndrome), nonfunctional islet cell tumor, somatostatinomas, and VIPomas.

**[0109]** The recipient animals are mammals, for example, mammals including primates, pet animals, livestock, and sport animals and are particularly preferably humans, dogs, and cats.

**[0110]** In the case of using the antibody of the present invention as a pharmaceutical composition, the pharmaceutical composition can be formulated by a method generally known to those skilled in the art. For example, the pharmaceutical composition can be used in the form of a parenteral injection of an aseptic solution or suspension with water or any other pharmaceutically acceptable liquid. For example, the pharmaceutical composition may be formulated with the antibody mixed in a unit dosage form required for generally accepted pharmaceutical practice, in appropriate combination with pharmacologically acceptable carriers or media, specifically, sterilized water, physiological saline, plant oil, an emulsifier, a suspending agent, a surfactant, a stabilizer, a flavoring agent, an excipient, a vehicle, a preservative, a binder, etc. The amount of the active ingredient in such a preparation is determined such that an appropriate dose within the prescribed range can be achieved.

**[0111]** An aseptic composition for injection can be formulated according to conventional pharmaceutical practice using a vehicle such as injectable distilled water.

**[0112]** Examples of aqueous solutions for injection include physiological saline, isotonic solutions containing glucose and other adjuvants, for example, D-sorbitol, D-mannose, D-mannitol, and sodium chloride. These solutions may be used in combination with an appropriate solubilizer, for example, an alcohol (specifically, ethanol) or a polyalcohol (e.g., propylene glycol and polyethylene glycol), or a nonionic surfactant, for example, polysorbate 80 (TM) or HCO-60.

**[0113]** Examples of oily solutions include sesame oil and soybean oil. These solutions may be used in combination with a solubilizer such as benzyl benzoate or benzyl alcohol. The solutions may be further mixed with a buffer (e.g., a phosphate buffer solution and a sodium acetate buffer solution), a soothing agent (e.g., procaine hydrochloride), a stabilizer (e.g., benzyl alcohol and phenol), or an antioxidant. The injection solutions thus prepared are usually charged into appropriate ampules.

**[0114]** The pharmaceutical composition of the present invention is administered orally or parenterally, preferably parenterally. Specific examples of its dosage forms include injections, intranasal administration agents, transpulmonary administration agents, and percutaneous administration agents. Examples of the injections include intravenous injection, intramuscular injection, intraperitoneal injection, and subcutaneous injection, through which the pharmaceutical composition can be administered systemically or locally.

**[0115]** Also, the administration method can be appropriately selected depending on the age, weight, sex, symptoms, etc. of a patient. The dose of a pharmaceutical composition containing the antibody or a polynucleotide encoding the antibody can be selected within a range of, for example, 0.0001 to 1000 mg/kg of body weight per dose. Alternatively, the dose can be selected within a range of, for example, 0.001 to 100000 mg/body of a patient, though the dose is not necessarily limited to these numeric values. Although the dose and the administration method vary depending on the weight, age, sex, symptoms, etc. of a patient, those skilled in the art can appropriately select the dose and the method.

**[0116]** The pharmaceutical composition of the present invention can be administered to a subject to treat pancreatic cancer.

**[0117]** The present invention further encompasses means, as defined in the claims, for treating pancreatic cancer, by administering the pharmaceutical composition of the present invention in combination with the antitumor agent as exemplified above or a pharmaceutical composition comprising the antitumor agent to a subject. The antibody of the present invention or the fragment thereof may be administered simultaneously with or separately from the antitumor agent to the subject. In the case of separately administering these pharmaceutical compositions, either one may be administered first or later. Their dosing intervals, doses, administration routes, and the number of doses can be appropriately selected by a specialist. The dosage forms of separate drugs to be administered simultaneously also include, for example, pharmaceutical compositions each formulated by mixing the antibody of the present invention or fragment thereof and the antitumor agent in a pharmacologically acceptable carrier (or medium). The above descriptions about prescription, formulation, administration routes, doses, cancer, etc. as to the pharmaceutical compositions and dosage forms containing the antibody of the present invention are also applicable to any of the above-described pharmaceutical compositions and dosage forms containing the antitumor agent. Thus, the present invention also provides a pharmaceutical combination (also referred to as a "pharmaceutical kit") for treatment of pancreatic cancer, comprising the pharmaceutical composition of the present invention and a pharmaceutical composition comprising the antitumor agent as exemplified above.

**[0118]** The present invention also provides a pharmaceutical composition for treatment of pancreatic cancer, comprising the antibody of the present invention or fragment thereof and the antitumor agent together with a pharmacologically acceptable carrier.

**[0119]** Alternatively, the antitumor agent may be conjugated with the antibody of the present invention or fragment

thereof. The resulting conjugate can be mixed with a pharmacologically acceptable carrier (or medium) as described above and formulated into a pharmaceutical composition.

## Examples

**[0120]** Hereinafter, the present invention will be described specifically with reference to Examples. However, the scope of the present invention is not intended to be limited by these specific examples.

[Example 1] Identification of pancreatic cancer antigenic protein by SEREX method

### (1) Preparation of cDNA library

**[0121]** Total RNAs were extracted from the testicular tissue of a healthy dog by the acid guanidium-phenol-chloroform method. Poly-A RNAs were purified using Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) according to the protocol attached to the kit.

**[0122]** The mRNAs (5  $\mu$ g) thus obtained were used to synthesize a canine testicular cDNA phage library. The cDNA phage library was prepared using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by Stratagene Corp.) according to the protocols attached to the kits. The prepared cDNA phage library had a size of  $7.73 \times 10^5$  pfu/ml.

### (2) Screening of cDNA library using serum

**[0123]** The canine testicular cDNA phage library thus prepared was used in immunoscreening. Specifically, host *E. coli* (XL1-Blue MRF') was infected by the phages on a NZY agarose plate ( $\phi 90 \times 15$  mm) so as to give 2210 clones. The host was cultured at 42°C for 3 to 4 hours to form plaques. The plate was covered at 37°C for 4 hours with a nitrocellulose membrane (Hybond C Extra; manufactured by GE Healthcare Bio-Sciences Ltd.) infiltrated with IPTG (isopropyl- $\beta$ -D-thiogalactopyranoside) for protein induction and expression to transfer the proteins to the membrane. Then, the membrane was recovered, dipped in TBS (10 mM tris-HCl, 150 mM NaCl, pH 7.5) containing 0.5% skimmed milk, and shaken overnight at 4°C to suppress nonspecific reaction. This filter was reacted with 500-fold diluted serum of an affected dog at room temperature for 2 to 3 hours.

**[0124]** The above serum of an affected dog used was serum collected from a breast cancer-affected dog. The serum was stored at -80°C and pretreated immediately before use. The serum pretreatment was performed by the following method: host *E. coli* (XL1-Blue MRF') was infected by  $\lambda$  ZAP Express phages having no foreign gene insert and then cultured overnight on a NZY plate medium at 37°C. Subsequently, a 0.2 M NaHCO<sub>3</sub> (pH 8.3) buffer containing 0.5 M NaCl was added to the plate. The plate was left standing at 4°C for 15 hours. Then, the supernatant was recovered as an *E. coli*/phage extract. Next, the recovered *E. coli*/phage extract was applied to a NHS-column (manufactured by GE Healthcare Bio-Sciences Ltd.) to immobilize *E. coli*/phage-derived proteins thereon. The serum of an affected dog was applied to this protein-immobilized column and reacted therewith. Antibodies adsorbed on the *E. coli* and the phages were removed from the serum. A serum fraction that had passed through the column was diluted 500-fold with TBS containing 0.5% skimmed milk. This dilution was used as an immunoscreening material.

**[0125]** The membrane blotted with the serum thus treated and the fusion proteins was washed four times with TBS-T (0.05% Tween 20/TBS) and then reacted at room temperature for 1 hour with secondary antibodies goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated; manufactured by BETHYL Laboratories, Inc.) diluted 5000-fold with TBS containing 0.5% skimmed milk, followed by detection through enzymatic color reaction using NBT/BCIP Stock Solution (manufactured by Roche Diagnostics K.K.). Colonies that matched with color reaction-positive sites were collected from the NZY agarose plate ( $\phi 90 \times 15$  mm) and lysed in 500  $\mu$ l of an SM buffer solution (100 mM NaCl, 10 mM MgClSO<sub>4</sub>, 50 mM tris-HCl, 0.01% gelatin, pH 7.5). Secondary screening and tertiary screening were subsequently performed in the same way as above until single color reaction-positive colonies were obtained. In this way, 30940 phage clones reactive with IgG in the serum were screened for. Then, 5 positive clones were isolated.

### (3) Homology search for isolated antigen gene

**[0126]** In order to subject these five positive clones thus isolated to nucleotide sequence analysis, procedures of converting the phage vectors to plasmid vectors were performed. Specifically, 200  $\mu$ l of a host *E. coli* (XL1-Blue MRF') solution prepared such that absorbance OD<sub>600</sub> became 1.0 was mixed with 250  $\mu$ l of a purified phage solution and further with 1  $\mu$ l of ExAssist helper phage (manufactured by Stratagene Corp.), followed by reaction at 37°C for 15 minutes. Then, 3 ml of an LB medium was added to the reaction mixture. The host was cultured at 37°C for 2.5 to 3 hours, immediately thereafter incubated for 20 minutes in a water bath of 70°C, and then centrifuged at  $1000 \times g$  at 4°C

for 15 minutes to recover the supernatant as a phagemid solution. Subsequently, 200  $\mu$ l of a phagemid host *E. coli* (SOLR) solution prepared such that absorbance OD600 became 1.0 was mixed with 10  $\mu$ l of a purified phage solution, followed by reaction at 37°C for 15 minutes. 50  $\mu$ l of the reaction mixture was inoculated to an LB agar medium containing ampicillin (final concentration: 50  $\mu$ g/ml) and cultured overnight at 37°C. A single colony of transformed SOLR was collected and cultured at 37°C in an LB medium containing ampicillin (final concentration: 50  $\mu$ g/ml). Then, plasmid DNAs having the inserts of interest were purified using QIAGEN plasmid Miniprep Kit (manufactured by Qiagen N.V.).

**[0127]** The full-length sequences of the inserts in the purified plasmids were analyzed by the primer walking method using a T3 primer represented by SEQ ID NO: 31 and a T7 primer represented by SEQ ID NO: 32. This sequencing analysis yielded gene sequences represented by SEQ ID NOs: 5, 7, 9, 11, and 13. As a result of conducting homology search with known genes using the nucleotide sequences of these genes and amino acid sequences (SEQ ID NOs: 6, 8, 10, 12, and 14) encoded thereby and the homology search program BLAST Search (<http://www.ncbi.nlm.nih.gov/BLAST/>), the obtained five genes were all found to be genes encoding CAPRIN-1. The sequence identity among these five genes was 100% for their nucleotide sequences in regions to be translated into proteins and 99% for their amino acid sequences. The sequence identity of these genes to genes encoding human homologous factors was 94% for their nucleotide sequences in regions to be translated into proteins and 98% for their amino acid sequences. The nucleotide sequences of the human homologous factors are represented by SEQ ID NOs: 1 and 3, and their amino acid sequences are represented by SEQ ID NOs: 2 and 4. Also, the sequence identity of the obtained canine genes to a gene encoding a bovine homologous factor was 94% for their nucleotide sequences in regions to be translated into proteins and 97% for their amino acid sequences. The nucleotide sequence of the bovine homologous factor is represented by SEQ ID NO: 15, and its amino acid sequence is represented by SEQ ID NO: 16. In this context, the sequence identity between the genes encoding the human homologous factors and the gene encoding the bovine homologous factor was 94% for their nucleotide sequences in regions to be translated into proteins and 93 to 97% for their amino acid sequences. The sequence identity of the obtained canine genes to a gene encoding a horse homologous factor was 93% for their nucleotide sequences in regions to be translated into proteins and 97% for their amino acid sequences. The nucleotide sequence of the horse homologous factor is represented by SEQ ID NO: 17, and its amino acid sequence is represented by SEQ ID NO: 18. In this context, the sequence identity between the genes encoding the human homologous factors and the gene encoding the horse homologous factor was 93% for their nucleotide sequences in regions to be translated into proteins and 96% for their amino acid sequences. The sequence identity of the obtained canine genes to genes encoding mouse homologous factors was 87 to 89% for their nucleotide sequences in regions to be translated into proteins and 95 to 97% for their amino acid sequences. The nucleotide sequences of the mouse homologous factors are represented by SEQ ID NOs: 19, 21, 23, 25, and 27, and their amino acid sequences are represented by SEQ ID NOs: 20, 22, 24, 26, and 28. In this context, the sequence identity between the genes encoding the human homologous factors and the genes encoding the mouse homologous factors was 89 to 91% for their nucleotide sequences in regions to be translated into proteins and 95 to 96% for their amino acid sequences. The sequence identity of the obtained canine genes to a gene encoding a chicken homologous factor was 82% for their nucleotide sequences in regions to be translated into proteins and 87% for their amino acid sequences. The nucleotide sequence of the chicken homologous factor is represented by SEQ ID NO: 29, and its amino acid sequence is represented by SEQ ID NO: 30. In this context, the sequence identity between the genes encoding the human homologous factors and the gene encoding the chicken homologous factor was 81 to 82% for their nucleotide sequences in regions to be translated into proteins and 86% for their amino acid sequences.

#### (4) Analysis of CAPRIN-1 gene expression in human pancreatic cancer cell

**[0128]** The genes thus obtained were examined for their expression in four different human pancreatic cancer cell lines (Capan-2, MIAPaCa-2, PANC-1, and BxPC-3) by RT-PCR. Reverse transcription reaction was performed as follows: total RNAs were extracted from 50 to 100 mg of each tissue and 5 to 10  $\times 10^6$  cells of each cell line using TRIZOL reagent (manufactured by Invitrogen Corp.) according to the protocol attached thereto. From the total RNAs, cDNAs were synthesized using Superscript First-Strand Synthesis System for RT-PCR (manufactured by Invitrogen Corp.) according to the protocol attached thereto. PCR reaction was performed as follows using primers (SEQ ID NOs: 33 and 34) specific for the obtained genes: PCR was performed by 30 repetitive cycles each involving 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds using Thermal Cycler (manufactured by Bio-Rad Laboratories, Inc.) and a reaction solution with the total amount adjusted to 25  $\mu$ l by the addition of 0.25  $\mu$ l of the sample prepared by the reverse transcription reaction and each reagent and attached buffer (2  $\mu$ M each of the primers, 0.2 mM each of dNTPs, and 0.65 U of ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.)). The above gene-specific primers were designed to amplify a region of nucleotide numbers 698 to 1124 in the nucleotide sequence (human CAPRIN-1 gene) of SEQ ID NO: 1. GAPDH-specific primers (SEQ ID NOs: 35 and 36) were also used for a comparative control. As a result, the gene expression was confirmed in all the human pancreatic cancer cell lines.

[Example 2] Preparation of polyclonal antibody against human CAPRIN-1

**[0129]** 1 mg of human CAPRIN-1 recombinant proteins prepared according to Example 3 of WO2010/016526 was mixed with an equal volume of an incomplete Freund's adjuvant (IFA) solution. This mixture was subcutaneously administered to each rabbit four times every two weeks. Then, blood was collected to obtain antiserum containing polyclonal antibodies. This antiserum was further purified using a protein G carrier (manufactured by GE Healthcare Bio-Sciences Ltd.) to obtain polyclonal antibodies against CAPRIN-1. In addition, the serum of a rabbit that received no antigen was purified using a protein G carrier in the same way as above and used as control antibodies.

[Example 3] Analysis of CAPRIN-1 protein expression in human pancreatic cancer

(1) Analysis of CAPRIN-1 protein expression on human pancreatic cancer cell

**[0130]** The four human pancreatic cancer cell lines (Capan-2, MIAPaCa-2, PANC-1, and BxPC-3) confirmed to have CAPRIN-1 gene expression were examined for their expression of CAPRIN-1 proteins on the cell surface.  $10^6$  cells of each human pancreatic cancer cell line thus confirmed to have gene expression were centrifuged in a 1.5-ml microcentrifuge tube. 2  $\mu$ g (5  $\mu$ l) of the anti-CAPRIN-1 polyclonal antibodies prepared in Example 2 was added thereto. The mixture was suspended in PBS containing 95  $\mu$ l of 0.1% fetal bovine serum and then left standing for 1 hour on ice. After washing with PBS, the resulting suspension was suspended in PBS containing 5  $\mu$ l of FITC-labeled goat anti-rabbit IgG antibodies (manufactured by Santa Cruz Biotechnology, Inc.) and 95  $\mu$ l of 0.1% fetal bovine serum (FBS) and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using the control antibodies prepared in Example 2 instead of the polyclonal antibodies against CAPRIN-1 to prepare a control. As a result, the pancreatic cancer cells supplemented with the anti-human CAPRIN-1 polyclonal antibodies all exhibited fluorescence intensity at least 20% stronger than that of the control. This demonstrated that CAPRIN-1 proteins are expressed on the cell membrane surface of the human pancreatic cancer cell lines. The above rate of enhancement in fluorescence intensity was indicated by the rate of increase in mean fluorescence intensity (MFI) in each cell line and calculated according to the following expression:

$$\text{Rate of increase in mean fluorescence intensity (Rate of enhancement in fluorescence intensity) (\%)} = ((\text{MFI of cells reacted with the anti-human CAPRIN-1 antibody}) - (\text{Control MFI})) / (\text{Control MFI}) \times 100$$

(2) Expression of CAPRIN-1 protein in human pancreatic cancer tissue

**[0131]** 40 pancreatic cancer tissue samples of a paraffin-embedded human pancreatic cancer tissue array (manufactured by US Biomax, Inc.) were used in immunohistochemical staining. The human pancreatic cancer tissue array was treated at 60°C for 3 hours and then placed in a staining bottle filled with xylene, and procedures of replacing xylene with a fresh one every 5 minutes were performed three times. Next, similar operation was performed using ethanol and PBS-T instead of xylene. The human pancreatic cancer tissue array was placed in a staining bottle filled with a 10 mM citrate buffer solution (pH 6.0) containing 0.05% Tween 20, treated at 125°C for 5 minutes, and then left standing at room temperature for 40 minutes or longer. Redundant water around each section was wiped off with Kimwipe. The section on a glass slide was encircled with a Dako pen, and an appropriate amount of Peroxidase Block (manufactured by Dako Japan Inc.) was added dropwise thereto. The glass slide was left standing at room temperature for 5 minutes and then placed in a staining bottle filled with PBS-T, and procedures of replacing PBS-T with a fresh one every 5 minutes were performed three times. A PBS-T solution containing 10% FBS was applied thereto as a blocking solution, and the glass slide was left standing at room temperature for 1 hour in a moist chamber. The anti-CAPRIN-1 polyclonal antibodies prepared in Example 2 were prepared into 10  $\mu$ g/ml solution with a PBS-T solution containing 5% FBS, and this solution was applied thereto. The glass slide was left standing overnight at 4°C in a moist chamber and washed with PBS-T for 10 minutes three times. Then, an appropriate amount of Peroxidase Labelled Polymer Conjugated (manufactured by Dako Japan Inc.) was added dropwise thereto, and the glass slide was left standing at room temperature for 30 minutes in a moist chamber. After washing with PBS-T for 10 minutes three times, a DAB staining solution (manufactured by Dako Japan Inc.) was applied thereto, and the glass slide was left standing at room temperature for approximately 10 minutes. Then, the staining solution was discarded, and the glass slide was washed with PBS-T for 10 minutes three times, then rinsed with distilled water, placed in 70%, 80%, 90%, 95%, and 100% ethanol solutions in this order for 1 minute per solution, and then left standing overnight in xylene. The glass slide was taken out and enclosed in Glycergel

Mounting Medium (manufactured by Dako Japan Inc.), followed by observation. As a result, the strong expression of CAPRIN-1 was confirmed in 36 (90%) out of a total of 40 pancreatic cancer tissue samples.

[Example 4] Antitumor effect (ADCC activity) of anti-CAPRIN-1 polyclonal antibody on pancreatic cancer cell

**[0132]** The antibody against CAPRIN-1 was studied for its ability to damage pancreatic cancer cells expressing CAPRIN-1. The polyclonal antibodies against human CAPRIN-1 obtained in Example 2 were used in this evaluation.  $10^6$  cells each of the human pancreatic cancer cell lines Capan-2 and MIA PaCa-2 confirmed to have CAPRIN-1 expression were collected into a 50-ml centrifuge tube, to which 100  $\mu$ Ci of chromium 51 was then added, followed by incubation at 37°C for 2 hours. Then, the cells were washed three times with an RPMI1640 medium containing 10% fetal calf serum and added at a density of  $10^3$  cells/well to a 96-well V-bottom plate. The polyclonal antibodies against human CAPRIN-1 were added thereto at a concentration of 1  $\mu$ g/well. Lymphocytes separated from human peripheral blood were further added thereto at a density of  $2 \times 10^5$  cells/well and cultured at 37°C for 4 hours under conditions of 5% CO<sub>2</sub>. After the culture, the amount of chromium (Cr) 51 released from damaged tumor cells was measured in the culture supernatant to calculate the ADCC activity of the anti-human CAPRIN-1 polyclonal antibodies against each pancreatic cancer cell line. As a result, the addition of the polyclonal antibodies against human CAPRIN-1 was confirmed to produce ADCC activity of 14% and 11% against Capan-2 and MIA PaCa-2, respectively, whereas similar operations produced ADCC activity less than 0.7% against both Capan-2 and MIA PaCa-2 using control antibodies prepared from antigen-unimmunized rabbit peripheral blood and produced ADCC activity less than 0.5% even in the absence of antibodies. These results demonstrated that the antibody against CAPRIN-1 can damage CAPRIN-1-expressing pancreatic cancer cells through its ADCC activity. These results about cytotoxic activity were obtained by: mixing the antibody against CAPRIN-1 used in the present invention, lymphocytes, and  $10^3$  tumor cells with incorporated chromium 51, as described above: culturing the cells for 4 hours; after the culture, measuring the amount of chromium 51 released into the medium; and calculating the cytotoxic activity against the tumor cells according to the following equation for calculation\*:

\*Equation: Cytotoxic activity (%) = Amount of chromium 51 released from the tumor cells supplemented with the antibody against CAPRIN-1 and lymphocytes / Amount of chromium 51 released from tumor cells supplemented with 1 N hydrochloric acid  $\times$  100.

[Example 5] Preparation of mouse and chicken monoclonal antibodies against CAPRIN-1

**[0133]** 100  $\mu$ g of the human CAPRIN-1 recombinant proteins prepared in Example 2 was mixed with an equal amount of MPL+TDM adjuvant (manufactured by Sigma-Aldrich Corp.). This mixture was used as an antigen solution per mouse. The antigen solution was intraperitoneally administered to each 6-week-old Balb/c mouse (manufactured by Japan SLC, Inc.). Then, 3 and 24 boosters were performed every 1 week to complete immunization. Three days after the final shot, the spleen of each mouse was excised and ground between two sterilized glass slides. Procedures of washing with PBS(-) (manufactured by Nissui Pharmaceutical Co., Ltd.) and removing the supernatant by centrifugation at 1500 rpm for 10 minutes were repeated three times to obtain spleen cells. The obtained spleen cells were mixed with mouse myeloma cells SP2/0 (purchased from ATCC) at a ratio of 10:1. 200  $\mu$ l of an RPMI1640 medium containing 10% FBS was heated to 37°C and mixed with 800  $\mu$ l of PEG1500 (manufactured by Boehringer Ingelheim GmbH), and the PEG solution thus prepared was added to the cell mixture, which was then left standing for 5 minutes for cell fusion. After removal of the supernatant by centrifugation at 1700 rpm for 5 minutes, the cells were suspended in 150 ml of an RPMI1640 medium containing 15% FBS supplemented with 2% equivalent of a HAT solution (manufactured by Life Technologies, Inc./Gibco) (HAT selective medium). This suspension was inoculated to fifteen 96-well plates (manufactured by Thermo Fisher Scientific Inc./Nunc) at a concentration of 100  $\mu$ l/well. The spleen cells and the myeloma cells were fused by culture at 37°C for 7 days under conditions of 5% CO<sub>2</sub> to obtain hybridomas.

**[0134]** The prepared hybridomas were screened with the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 proteins as an indicator. A 1  $\mu$ g/ml solution of the CAPRIN-1 proteins prepared in Example 2 was added to a 96-well plate at a concentration of 100  $\mu$ l/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% bovine serum albumin (BSA) solution (manufactured by Sigma-Aldrich Corp.) was added thereto at a concentration of 400  $\mu$ l/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400  $\mu$ l of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added to the well at a concentration of 100  $\mu$ l/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-mouse IgG (H+L) antibodies (manufactured by Invitrogen Corp.) diluted 5000-fold with PBS were added to the well at a concentration of 100  $\mu$ l/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a

TMB substrate solution (manufactured by Thermo Fisher Scientific Inc.) was added thereto at a concentration of 100  $\mu$ l/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at a concentration of 100  $\mu$ l/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, several hybridomas producing antibodies having high absorbance were selected.

**[0135]** The selected hybridomas were added to a 96-well plate at a density of 0.5 cells/well and cultured in the plate. One week later, hybridomas forming single colonies in the wells were observed. The cells in these wells were further cultured, and the cloned hybridomas were screened with the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 proteins as an indicator. A 1  $\mu$ g/ml solution of the CAPRIN-1 proteins prepared in Example 2 was added to a 96-well plate at a concentration of 100  $\mu$ l/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% BSA solution was added to the well at a concentration of 400  $\mu$ l/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400  $\mu$ l of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added to the well at a concentration of 100  $\mu$ l/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-mouse IgG (H+L) antibodies (manufactured by Invitrogen Corp.) diluted 5000-fold with PBS were added to the well at a concentration of 100  $\mu$ l/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (manufactured by Thermo Fisher Scientific Inc.) was added to the well at a concentration of 100  $\mu$ l/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at a concentration of 100  $\mu$ l/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, 150 hybridoma lines producing mouse monoclonal antibodies reactive with CAPRIN-1 proteins were obtained.

**[0136]** Next, these mouse monoclonal antibodies were screened for antibodies reactive with the surface of cancer cells expressing CAPRIN-1. Specifically, 10<sup>6</sup> cells of a human breast cancer cell line MDA-MB-231 V were centrifuged in a 1.5-ml microcentrifuge tube. 100  $\mu$ l of the culture supernatant of each hybridoma obtained above was added thereto and left standing for 1 hour on ice. After washing with PBS, FITC-labeled goat anti-mouse IgG antibodies (manufactured by Invitrogen Corp.) diluted 500-fold with PBS containing 0.1% FBS were added thereto and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using the serum of each untreated 6-week-old Balb/c mouse diluted 500-fold with a medium for hybridoma culture, instead of the antibodies, to prepare a control. As a result, 22 mouse monoclonal antibodies (mouse monoclonal antibodies #1 to #22) having stronger fluorescence intensity than that of the control, i.e., reactive with the surface of breast cancer cells, were selected.

**[0137]** In order to prepare chicken monoclonal antibodies, 300  $\mu$ g of the antigenic proteins (human CAPRIN-1) (SEQ ID NO: 2) prepared in Example 2 was mixed with an equal amount of a complete Freund's adjuvant. This mixture was used as an antigen solution per chicken. The antigen solution was intraperitoneally administered to each 7-week-old chicken. Then, 7 boosters were performed every 4 weeks to complete immunization. Four days after the final shot, the spleen of each chicken was excised and ground between two sterilized glass slides. Procedures of washing with PBS(-) (manufactured by Nissui Pharmaceutical Co., Ltd.) and removing the supernatant by centrifugation at 1500 rpm for 10 minutes were repeated three times to obtain spleen cells. The obtained spleen cells were mixed with light chain-deficient chicken myeloma cells established from chickens by transformation using avian reticuloendotheliosis virus, at a ratio of 5:1. 200  $\mu$ l of an IMDM medium containing 10% FBS was heated to 37°C and mixed with 800  $\mu$ l of PEG1500 (manufactured by Boehringer Ingelheim GmbH), and the PEG solution thus prepared was added to the cell mixture, which was then left standing for 5 minutes for cell fusion. After removal of the supernatant by centrifugation at 1700 rpm for 5 minutes, the cells were suspended in 300 ml of an IMDM medium containing 10% FBS supplemented with 2% equivalent of a HAT solution (manufactured by Life Technologies, Inc./Gibco) (HAT selective medium). This suspension was inoculated to thirty 96-well plates (manufactured by Thermo Fisher Scientific Inc./Nunc) at a concentration of 100  $\mu$ l/well. The spleen cells and the chicken myeloma cells were fused by culture at 37°C for 7 days under conditions of 5% CO<sub>2</sub> to obtain hybridomas.

**[0138]** The prepared hybridomas were screened with the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 proteins as an indicator. A 1  $\mu$ g/ml solution of the CAPRIN-1 proteins prepared in Example 2 was added to a 96-well plate at a concentration of 100  $\mu$ l/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% bovine serum albumin (BSA) solution (manufactured by Sigma-Aldrich Corp.) was added thereto at a concentration of 400  $\mu$ l/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400  $\mu$ l of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at a concentration of 100  $\mu$ l/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-chicken IgY antibodies (manufactured by Sigma-Aldrich Corp.) diluted 5000-fold with PBS were added to the well at a concentration of 100  $\mu$ l/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (manufactured by Thermo Fisher Scientific Inc.) was added to the well at a concentration of 100  $\mu$ l/well

and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at a concentration of 100  $\mu$ l/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, several hybridomas producing antibodies having high absorbance were selected.

**[0139]** The selected hybridomas were added to a 96-well plate at a density of 0.5 cells/well and cultured in the plate. One week later, hybridomas forming single colonies in the wells were observed. The cells in these wells were further cultured, and the cloned hybridomas were screened with the binding affinity of antibodies produced by the hybridomas against CAPRIN-1 proteins as an indicator. A 1  $\mu$ g/ml solution of the human CAPRIN-1 proteins was added to a 96-well plate at a concentration of 100  $\mu$ l/well and left standing at 4°C for 18 hours. Each well was washed three times with PBS-T. Then, a 0.5% BSA solution was added to the well at a concentration of 400  $\mu$ l/well and left standing at room temperature for 3 hours. The solution in each well was discarded, and each well was washed three times with 400  $\mu$ l of PBS-T. Then, the culture supernatant of each hybridoma obtained above was added thereto at a concentration of 100  $\mu$ l/well and left standing at room temperature for 2 hours. Each well was washed three times with PBS-T. Then, HRP-labeled anti-chicken IgY antibodies (manufactured by Sigma-Aldrich Corp.) diluted 5000-fold with PBS were added to the well at a concentration of 100  $\mu$ l/well and left standing at room temperature for 1 hour. Each well was washed three times with PBS-T. Then, a TMB substrate solution (manufactured by Thermo Fisher Scientific Inc.) was added to the well at a concentration of 100  $\mu$ l/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at a concentration of 100  $\mu$ l/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, several hybridoma lines producing monoclonal antibodies reactive with CAPRIN-1 proteins were obtained.

**[0140]** Next, these monoclonal antibodies were screened for antibodies reactive with the surface of cancer cells expressing CAPRIN-1. Specifically,  $5 \times 10^5$  cells of a human breast cancer cell line MDA-MB-231V were centrifuged in a 1.5-ml microcentrifuge tube. 100  $\mu$ l of the culture supernatant of each hybridoma obtained above was added thereto and left standing for 1 hour on ice. After washing with PBS, FITC-labeled goat anti-chicken IgG (H+L) antibodies (manufactured by SouthernBiotech) diluted 30-fold with PBS containing 0.1% FBS were added thereto and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using a medium for hybridoma culture to prepare a control sample. As a result, 3 monoclonal antibodies (chicken monoclonal antibodies #1, #2, and #3) having stronger fluorescence intensity than that of the control, i.e., reactive with the surface of breast cancer cells expressing CAPRIN-1, were selected.

[Example 6] Characterization of selected antibody

(1) Cloning of variable region gene of anti-CAPRIN-1 monoclonal antibody

**[0141]** mRNAs were extracted from the hybridoma line producing each of the 22 mouse monoclonal antibodies and 3 chicken monoclonal antibodies selected in Example 5. Genes of heavy chain variable (VH) and light chain variable (VL) regions of all the anti-CAPRIN-1 monoclonal antibodies were obtained by RT-PCR using primers specific for mouse FR1- and FR4-derived sequences for the mouse monoclonal antibody-producing hybridomas and primers specific for chicken FR1- and FR4-derived sequences for the chicken monoclonal antibody-producing hybridomas. For sequencing, these genes were cloned into pCR2.1 vectors (manufactured by Invitrogen Corp.).

(1)-1 RT-PCR

**[0142]** mRNAs were prepared from  $10^6$  cells of each mouse monoclonal antibody-producing hybridoma line using mRNA micro purification kit (manufactured by GE Healthcare Bio-Sciences Ltd.) and reverse-transcribed using Super-Script II 1st strand synthesis kit (manufactured by Invitrogen Corp.) to synthesis cDNAs. These procedures were performed according to the protocol attached to each kit. The antibody genes were amplified by PCR using the obtained cDNAs. A mouse heavy chain FR1 sequence-specific primer (SEQ ID NO: 257) and a mouse heavy chain FR4 sequence-specific primer (SEQ ID NO: 258) were used for obtaining the VH region genes. Also, a mouse light chain FR1 sequence-specific primer (SEQ ID NO: 259) and a mouse light chain FR4-specific primer (SEQ ID NO: 260) were used for obtaining the VL region genes. These primers were designed with reference to Jones, S.T. and Bending, M.M. Bio/Technology 9, 88-89 (1991). PCR employed Ex Taq (manufactured by Takara Bio Inc.). The cDNA sample was added to 5  $\mu$ l of 10  $\times$  EX Taq Buffer, 4  $\mu$ l of dNTP Mixture (2.5 mM), 2  $\mu$ l each of the primers (1.0  $\mu$ M), and 0.25  $\mu$ l of Ex Taq (5 U/ $\mu$ l), and the total amount of the solution was adjusted to 50  $\mu$ l with sterilized water. After treatment at 94°C for 2 minutes, PCR was performed under conditions of 30 cycles each involving a combination of denaturation at 94°C for 1 minute, annealing at 58°C for 30 seconds, and elongation reaction at 72°C for 1 minute.

**[0143]** Also, total RNA was extracted from  $10^6$  cells of each chicken monoclonal antibody-producing hybridoma line

using High Pure RNA Isolation Kit (manufactured by Roche Diagnostics K.K.). Then, cDNAs were synthesized using PrimeScript II 1st strand cDNA Synthesis Kit (manufactured by Takara Bio Inc.). These procedures were performed according to the protocol attached to each kit. The chicken antibody heavy and light chain variable region genes were separately amplified by PCR according to a routine method with the synthesized cDNAs as templates using KOD-Plus-DNA Polymerase (manufactured by Toyobo Co., Ltd.). A chicken heavy chain FR1 sequence-specific primer and a chicken heavy chain FR4 sequence-specific primer were used for obtaining the chicken antibody VH region genes. Also, a chicken light chain FR1 sequence-specific primer and a chicken light chain FR4-specific primer were used for obtaining the VL region genes.

#### (1)-2 Cloning

**[0144]** Each PCR product obtained above was electrophoresed on an agarose gel. DNA bands excised for each of the VH and VL regions. Each DNA fragment was purified using QIAquick Gel purification kit (manufactured by Qiagen N.V.) according to the protocol attached thereto. Each DNA thus purified was cloned into pCR2.1 vector using TA cloning kit (manufactured by Invitrogen Corp.). DH5a competent cells (manufactured by Toyobo Co., Ltd.) were transformed with the ligated vector according to a standard method. Ten clones of each transformant were cultured overnight at 37°C in a medium containing 100 µg/ml ampicillin. Then, each plasmid DNA was purified using Qiaspin Miniprep kit (manufactured by Qiagen N.V.).

#### (1)-3 Sequencing

**[0145]** The VH and VL region genes in each plasmid obtained above were sequenced using an M13 forward primer (SEQ ID NO: 261) and an M13 reverse primer (SEQ ID NO: 262), a fluorescence sequencer (DNA sequencer 3130XL manufactured by Applied Biosystems, Inc.), and BigDye Terminator Ver 3.1 Cycle Sequencing Kit (manufactured by Applied Biosystems, Inc.) according to the protocols attached thereto. As a result, the sequence of each gene and an amino acid sequence encoded thereby were determined.

**[0146]** Specifically, these monoclonal antibodies each comprise a heavy chain variable (VH) region having an amino acid sequence of SEQ ID NO: 40 (SEQ ID NO: 45), SEQ ID NO: 50 (SEQ ID NO: 55), SEQ ID NO: 60 (SEQ ID NO: 65), SEQ ID NO: 70 (SEQ ID NO: 75), SEQ ID NO: 80 (SEQ ID NO: 85), SEQ ID NO: 90 (SEQ ID NO: 95), SEQ ID NO: 100 (SEQ ID NO: 105), SEQ ID NO: 110 (SEQ ID NO: 115), SEQ ID NO: 120 (SEQ ID NO: 125), SEQ ID NO: 130 (SEQ ID NO: 131), SEQ ID NO: 135 (SEQ ID NO: 140), SEQ ID NO: 145 (SEQ ID NO: 150), SEQ ID NO: 160 (SEQ ID NO: 165), SEQ ID NO: 170 (SEQ ID NO: 175), SEQ ID NO: 200 (SEQ ID NO: 205), SEQ ID NO: 210 (SEQ ID NO: 215), SEQ ID NO: 220 (SEQ ID NO: 225), SEQ ID NO: 230 (SEQ ID NO: 235), SEQ ID NO: 240 (SEQ ID NO: 245), or SEQ ID NO: 250 (SEQ ID NO: 255) (SEQ ID NO in the parentheses represents a gene sequence) and a light chain variable (VL) region having an amino acid sequence of SEQ ID NO: 44 (SEQ ID NO: 46), SEQ ID NO: 54 (SEQ ID NO: 56), SEQ ID NO: 64 (SEQ ID NO: 66), SEQ ID NO: 74 (SEQ ID NO: 76), SEQ ID NO: 84 (SEQ ID NO: 86), SEQ ID NO: 94 (SEQ ID NO: 96), SEQ ID NO: 104 (SEQ ID NO: 106), SEQ ID NO: 114 (SEQ ID NO: 116), SEQ ID NO: 124 (SEQ ID NO: 126), SEQ ID NO: 139 (SEQ ID NO: 141), SEQ ID NO: 149 (SEQ ID NO: 151), SEQ ID NO: 155 (SEQ ID NO: 156), SEQ ID NO: 164 (SEQ ID NO: 166), SEQ ID NO: 174 (SEQ ID NO: 176), SEQ ID NO: 180 (SEQ ID NO: 181), SEQ ID NO: 185 (SEQ ID NO: 186), SEQ ID NO: 190 (SEQ ID NO: 191), SEQ ID NO: 195 (SEQ ID NO: 196), SEQ ID NO: 204 (SEQ ID NO: 206), SEQ ID NO: 214 (SEQ ID NO: 216), SEQ ID NO: 224 (SEQ ID NO: 226), SEQ ID NO: 234 (SEQ ID NO: 236), SEQ ID NO: 244 (SEQ ID NO: 246), or SEQ ID NO: 254 (SEQ ID NO: 256) (SEQ ID NO in the parentheses represents a gene sequence), wherein the VH region comprises CDR1 represented by an amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 47, SEQ ID NO: 57, SEQ ID NO: 67, SEQ ID NO: 77, SEQ ID NO: 87, SEQ ID NO: 97, SEQ ID NO: 107, SEQ ID NO: 117, SEQ ID NO: 127, SEQ ID NO: 132, SEQ ID NO: 142, SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, SEQ ID NO: 227, SEQ ID NO: 237, or SEQ ID NO: 247, CDR2 represented by an amino acid sequence of SEQ ID NO: 38, SEQ ID NO: 48, SEQ ID NO: 58, SEQ ID NO: 68, SEQ ID NO: 78, SEQ ID NO: 88, SEQ ID NO: 98, SEQ ID NO: 108, SEQ ID NO: 118, SEQ ID NO: 128, SEQ ID NO: 133, SEQ ID NO: 143, SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, SEQ ID NO: 228, SEQ ID NO: 238, or SEQ ID NO: 248, and CDR3 represented by an amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 49, SEQ ID NO: 59, SEQ ID NO: 69, SEQ ID NO: 79, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 109, SEQ ID NO: 119, SEQ ID NO: 129, SEQ ID NO: 134, SEQ ID NO: 144, SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, SEQ ID NO: 229, SEQ ID NO: 239, or SEQ ID NO: 249, and the VL region comprises CDR1 represented by an amino acid sequence of SEQ ID NO: 41, SEQ ID NO: 51, SEQ ID NO: 61, SEQ ID NO: 71, SEQ ID NO: 81, SEQ ID NO: 91, SEQ ID NO: 101, SEQ ID NO: 111, SEQ ID NO: 121, SEQ ID NO: 136, SEQ ID NO: 146, SEQ ID NO: 152, SEQ ID NO: 161, SEQ ID NO: 171, SEQ ID NO: 177, SEQ ID NO: 182, SEQ ID NO: 187, SEQ ID NO: 192, SEQ ID NO: 201, SEQ ID NO: 211, SEQ ID NO: 221, SEQ ID NO: 231, SEQ ID NO: 241, or SEQ ID NO: 251, CDR2 represented by an amino acid sequence of SEQ ID NO: 42, SEQ ID NO: 52, SEQ ID NO: 62, SEQ ID NO:

72, SEQ ID NO: 82, SEQ ID NO: 92, SEQ ID NO: 102, SEQ ID NO: 112, SEQ ID NO: 122, SEQ ID NO: 137, SEQ ID NO: 147, SEQ ID NO: 153, SEQ ID NO: 162, SEQ ID NO: 172, SEQ ID NO: 178, SEQ ID NO: 183, SEQ ID NO: 188, SEQ ID NO: 193, SEQ ID NO: 202, SEQ ID NO: 212, SEQ ID NO: 222, SEQ ID NO: 232, SEQ ID NO: 242, or SEQ ID NO: 252, and CDR3 represented by an amino acid sequence of SEQ ID NO: 43, SEQ ID NO: 53, SEQ ID NO: 63, SEQ ID NO: 73, SEQ ID NO: 83, SEQ ID NO: 93, SEQ ID NO: 103, SEQ ID NO: 113, SEQ ID NO: 123, SEQ ID NO: 138, SEQ ID NO: 148, SEQ ID NO: 154, SEQ ID NO: 163, SEQ ID NO: 173, SEQ ID NO: 179, SEQ ID NO: 184, SEQ ID NO: 189, SEQ ID NO: 194, SEQ ID NO: 203, SEQ ID NO: 213, SEQ ID NO: 223, SEQ ID NO: 233, SEQ ID NO: 243, or SEQ ID NO: 253.

**[0147]** The amino acid sequences of the heavy chain variable regions of the obtained monoclonal antibodies are represented by SEQ ID NOs: 40, 50, SEQ ID NO: 60, SEQ ID NO: 70, SEQ ID NO: 80, SEQ ID NO: 90, SEQ ID NO: 100, SEQ ID NO: 110, SEQ ID NO: 120, SEQ ID NO: 130, SEQ ID NO: 135, SEQ ID NO: 145, SEQ ID NO: 160, SEQ ID NO: 170, SEQ ID NO: 200, SEQ ID NO: 210, SEQ ID NO: 220, SEQ ID NO: 230, SEQ ID NO: 240, and SEQ ID NO: 250. The amino acid sequences of their light chain variable regions are represented by SEQ ID NO: 44, SEQ ID NO: 54, SEQ ID NO: 64, SEQ ID NO: 74, SEQ ID NO: 84, SEQ ID NO: 94, SEQ ID NO: 104, SEQ ID NO: 114, SEQ ID NO: 124, SEQ ID NO: 139, SEQ ID NO: 149, SEQ ID NO: 155, SEQ ID NO: 164, SEQ ID NO: 174, SEQ ID NO: 180, SEQ ID NO: 185, SEQ ID NO: 190, SEQ ID NO: 195, SEQ ID NO: 204, SEQ ID NO: 214, SEQ ID NO: 224, SEQ ID NO: 234, SEQ ID NO: 244, and SEQ ID NO: 254.

**[0148]** Specifically, the mouse monoclonal antibody #1 comprises the heavy chain variable region of SEQ ID NO: 70 and the light chain variable region of SEQ ID NO: 74; #2 comprises the heavy chain variable region of SEQ ID NO: 80 and the light chain variable region of SEQ ID NO: 84; #3 comprises the heavy chain variable region of SEQ ID NO: 90 and the light chain variable region of SEQ ID NO: 94; #4 comprises the heavy chain variable region of SEQ ID NO: 100 and the light chain variable region of SEQ ID NO: 104; #5 comprises the heavy chain variable region of SEQ ID NO: 110 and the light chain variable region of SEQ ID NO: 114; #6 comprises the heavy chain variable region of SEQ ID NO: 120 and the light chain variable region of SEQ ID NO: 124; #7 comprises the heavy chain variable region of SEQ ID NO: 130 and the light chain variable region of SEQ ID NO: 124; #8 comprises the heavy chain variable region of SEQ ID NO: 135 and the light chain variable region of SEQ ID NO: 139; #9 comprises the heavy chain variable region of SEQ ID NO: 145 and the light chain variable region of SEQ ID NO: 149; #10 comprises the heavy chain variable region of SEQ ID NO: 145 and the light chain variable region of SEQ ID NO: 155; #11 comprises the heavy chain variable region of SEQ ID NO: 160 and the light chain variable region of SEQ ID NO: 164; #12 comprises the heavy chain variable region of SEQ ID NO: 170 and the light chain variable region of SEQ ID NO: 174; #13 comprises the heavy chain variable region of SEQ ID NO: 170 and the light chain variable region of SEQ ID NO: 180; #14 comprises the heavy chain variable region of SEQ ID NO: 170 and the light chain variable region of SEQ ID NO: 185; #15 comprises the heavy chain variable region of SEQ ID NO: 170 and the light chain variable region of SEQ ID NO: 190; #16 comprises the heavy chain variable region of SEQ ID NO: 170 and the light chain variable region of SEQ ID NO: 195; #17 comprises the heavy chain variable region of SEQ ID NO: 200 and the light chain variable region of SEQ ID NO: 204; #18 comprises the heavy chain variable region of SEQ ID NO: 210 and the light chain variable region of SEQ ID NO: 214; #19 comprises the heavy chain variable region of SEQ ID NO: 220 and the light chain variable region of SEQ ID NO: 224; #20 comprises the heavy chain variable region of SEQ ID NO: 230 and the light chain variable region of SEQ ID NO: 234; #21 comprises the heavy chain variable region of SEQ ID NO: 240 and the light chain variable region of SEQ ID NO: 244; #22 comprises the heavy chain variable region of SEQ ID NO: 250 and the light chain variable region of SEQ ID NO: 254.

**[0149]** The amino acid sequences of the heavy chain variable regions of the obtained chicken monoclonal antibodies are represented by SEQ ID NOs: 40, 50, and 60. The amino acid sequences of their light chain variable regions are represented by SEQ ID NOs: 44, 54, and 64.

**[0150]** Specifically, the chicken monoclonal antibody #1 comprises the heavy chain variable region of SEQ ID NO: 40 and the light chain variable region of SEQ ID NO: 44, wherein the heavy chain variable region has CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NOs: 37, 38, and 39, respectively, and the light chain variable region has CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NOs: 41, 42, and 43, respectively; the chicken monoclonal antibody #2 comprises the heavy chain variable region of SEQ ID NO: 50 and the light chain variable region of SEQ ID NO: 54, wherein the heavy chain variable region has CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NOs: 47, 48, and 49, respectively, and the light chain variable region has CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NOs: 51, 52, and 53, respectively; and the chicken monoclonal antibody #3 comprises the heavy chain variable region of SEQ ID NO: 60 and the light chain variable region of SEQ ID NO: 64, wherein the heavy chain variable region has CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NOs: 57, 58, and 59, respectively, and the light chain variable region has CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NOs: 61, 62, and 63, respectively.

## (2) Preparation of human-chicken chimeric recombinant antibody and mouse-chicken chimeric antibody

**[0151]** The gene amplification fragment of the heavy chain variable region (SEQ ID NO: 40) of the chicken monoclonal antibody #1 obtained in the preceding paragraph (1) was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA4/myc-His (manufactured by Invitrogen Corp.) vector already having gene inserts of a chicken antibody-derived leader sequence comprising SEQ ID NO: 263 and a human IgG<sub>1</sub> H chain constant region comprising SEQ ID NO: 264. Also, the gene amplification fragment of the light chain variable region (SEQ ID NO: 44) of the chicken monoclonal antibody #1 was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA3.1/myc-His (manufactured by Invitrogen Corp.) vector already having gene inserts of a chicken antibody-derived leader sequence comprising SEQ ID NO: 263 and a human IgG<sub>1</sub> L chain constant region comprising SEQ ID NO: 265.

**[0152]** Next, the recombinant vector having the gene insert of the heavy chain variable region (SEQ ID NO: 40) of the chicken monoclonal antibody #1 and the recombinant vector having the gene insert of the light chain variable region (SEQ ID NO: 44) of the chicken monoclonal antibody #1 were introduced into CHO-K1 cells (obtained from Riken Cell Bank). Specifically,  $2 \times 10^5$  CHO-K1 cells were cultured in a Ham's F12 medium (manufactured by Invitrogen Corp.) containing 1 ml of 10% FBS per well of a 12-well culture plate, and washed with PBS(-). Then, a fresh Ham's F12 medium containing 1 ml of 10% FBS per well was added to the well. 250 ng each of the vectors lysed in 30  $\mu$ l of OptiMEM (manufactured by Invitrogen Corp.) was mixed with 30  $\mu$ l of Polyfect transfection reagent (manufactured by Qiagen N.V.), and this mixture was added to each well. The CHO-K1 cells cotransfected with the recombinant vectors were cultured in a Ham's F12 medium containing 10% FBS supplemented with 200  $\mu$ g/ml Zeocin (manufactured by Invitrogen Corp.) and 200  $\mu$ g/ml Geneticin (manufactured by Roche Diagnostics) and then inoculated to a 96-well plate at a density of 0.5 cells/well to prepare a cell line stably producing a human-chicken chimeric antibody #1 (#1) having the variable regions of the chicken monoclonal antibody #1. Cell lines stably producing a human-chicken chimeric antibody #2 (#2) or a human-chicken chimeric antibody #3 (#3) were also prepared in the same way as above as to the chicken monoclonal antibodies #2 and #3.

**[0153]** Each prepared cell line was cultured for 5 days in a 150-cm<sup>2</sup> flask at a density of  $5 \times 10^5$  cells/ml using 30 ml of a serum-free OptiCHO medium (manufactured by Invitrogen Corp.) to obtain culture supernatants containing #1, #2, or #3.

**[0154]** Likewise, the gene amplification fragment of the heavy chain variable region (SEQ ID NO: 40) of the chicken monoclonal antibody #1 was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA4/myc-His (manufactured by Invitrogen Corp.) vector already having gene inserts of a chicken antibody-derived leader sequence and a mouse IgG<sub>1</sub> H chain constant region. Also, the gene amplification fragment of the light chain variable region (SEQ ID NO: 44) of the chicken monoclonal antibody #1 was treated at both ends with restriction enzymes, then purified, and inserted according to a routine method into a pcDNA3.1/myc-His (manufactured by Invitrogen Corp.) vector already having gene inserts of a chicken antibody-derived leader sequence and a mouse IgG<sub>1</sub> L chain constant region. These recombinant vectors were introduced into CHO-K1 cells in the same way as above to prepare a cell line stably producing a mouse-chicken chimeric antibody #1 having the variable regions of the chicken monoclonal antibody #1. Cell lines stably producing a mouse-chicken chimeric antibody #2 (#2) or a mouse-chicken chimeric antibody #3 (#3) were also prepared in the same way as above as to the chicken monoclonal antibodies #2 and #3.

**[0155]** Each prepared cell line was cultured for 5 days in a 150-cm<sup>2</sup> flask at a density of  $5 \times 10^5$  cells/ml using 30 ml of a serum-free OptiCHO medium (manufactured by Invitrogen Corp.) to obtain culture supernatants containing the mouse-chicken chimeric antibody #1, the mouse-chicken chimeric antibody #2, or the mouse-chicken chimeric antibody #3.

## (3) Expression of CAPRIN-1 on pancreatic cancer cell surface using obtained monoclonal antibody

**[0156]** Next, four pancreatic cancer cell lines (Capan-2, MIAPaCa-2, PANC-1, and BxPC-3) confirmed to have CAPRIN-1 gene expression were examined for their expression of CAPRIN-1 protein on the cell surface.  $10^6$  cells of each cell line were centrifuged in each 1.5-ml microcentrifuge tube. The cancer cell surface-reactive anti-CAPRIN-1 mouse monoclonal antibodies #1 to #22 prepared in Example 4 and the culture supernatant (100  $\mu$ l) containing the anti-CAPRIN-1 mouse-chicken chimeric antibody #1, #2, or #3 prepared in the preceding paragraph (2) were separately added to the tubes and left standing for 1 hour on ice. After washing with PBS, the cells were suspended in FITC-labeled goat anti-mouse IgG antibodies (manufactured by Invitrogen Corp.) diluted 500-fold with PBS containing 0.1% FBS and left standing for 1 hour on ice. After washing with PBS, the fluorescence intensity was measured using FACSCalibur (Becton, Dickinson and Company). On the other hand, the same operation as above was performed using isotype control antibodies, instead of the anti-CAPRIN-1 mouse monoclonal antibodies #1 to #22 and the culture supernatant containing the mouse-chicken chimeric antibody #1, #2, or #3, to prepare a control. As a result, all the cells supplemented with any

of the monoclonal antibodies #1 to #22 and the mouse-chicken chimeric antibodies #1, #2, and #3 had fluorescence intensity at least 20% stronger than that of the control. As a specific example, Capan-2, MIAPaCa-2, PANC-1, and BxPC-3 supplemented with the mouse-chicken chimeric antibody #1 all exhibited 200% or higher enhancement in fluorescence intensity. This demonstrated that CAPRIN-1 proteins are expressed on the cell membrane surface of the human pancreatic cancer cell lines. The above rate of enhancement in fluorescence intensity was indicated by the rate of increase in mean fluorescence intensity (MFI) in each cell line and calculated according to the following expression:

$$\text{Rate of increase in mean fluorescence intensity (Rate of enhancement in fluorescence intensity) (\%)} = ((\text{MFI of cells reacted with the anti-human CAPRIN-1 antibody}) - (\text{Control MFI})) / (\text{Control MFI}) \times 100$$

(4) Antitumor effect (ADCC activity) of anti-CAPRIN-1 antibody on human pancreatic cancer cell

**[0157]** Of the antibodies obtained above, the human-chicken chimeric antibody #1 was used to evaluate its cytotoxic activity (ADCC activity) against human pancreatic cancer cells. The culture supernatant containing the human-chicken chimeric antibody #1 obtained in the paragraph (2) was purified using Hitrap Protein A Sepharose FF (manufactured by GE Healthcare Bio-Sciences Ltd.). After replacement with PBS(-), the solution was filtered through a 0.22- $\mu\text{m}$  filter (manufactured by Millipore Corp.). The resulting antibody was used for activity assay.  $10^6$  cells each of human pancreatic cancer cell lines MIAPaCa-2 and Capan-2 were collected into a 50-ml centrifuge tube, to which 100  $\mu\text{Ci}$  of chromium 51 was then added, followed by incubation at 37°C for 2 hours. Then, the cells were washed three times with an RPMI1640 medium containing 10% FBS and added at a density of  $2 \times 10^3$  cells/well to a 96-well V-bottom plate to prepare target cells. The purified antibody was added thereto at a concentration of 1.2  $\mu\text{g}$ /well. A cell population containing human NK cells was separated from human peripheral blood lymphocytes using the following approach: human peripheral blood mononuclear cells were reacted with FITC fluorescent dye-labeled antibodies (anti-human CD3 antibody, anti-human CD20 antibody, anti-human CD 19 antibody, anti-human CD11c antibody, or anti-HLA-DR antibody (Becton, and Dickinson and Company)). A cell population containing NK cells unstained with the antibodies was separated using a cell sorter (FACS Vantage SE (Becton, and Dickinson and Company)) or human NK cell separation kit (NK Cell Isolation Kit (manufactured by Miltenyi Biotec K.K.)). The obtained cell population containing NK cells was added to the plate at a density of  $2 \times 10^5$  cells/well and cultured at 37°C for 4 hours under conditions of 5%  $\text{CO}_2$ . After the culture, the amount of chromium (Cr) 51 released from damaged tumor cells was measured in the culture supernatant to calculate the ADCC activity of the anti-CAPRIN-1 antibody against the pancreatic cancer cells. As a result, the human-chicken chimeric antibody #1 exhibited 32% cytotoxic activity against MIAPaCa-2, whereas a cytotoxic activity less than 5% was obtained by using monoclonal antibodies reactive with the CAPRIN-1 protein itself but unreactive with the surface of cancer cells or in the absence of antibodies. Also, the human-chicken chimeric antibody #1 exhibited 20% or higher cytotoxic activity against Capan-2, whereas a cytotoxic activity less than 5% was obtained by using monoclonal antibodies reactive with the CAPRIN-1 protein itself but unreactive with the surface of cancer cells or in the absence of antibodies. The anti-CAPRIN-1 mouse monoclonal antibodies #1 to #22, the human-chicken chimeric antibody #2, and the human-chicken chimeric antibody #3 were also examined for their cytotoxic activity against MIAPaCa-2 and Capan-2 in the same way as above. As a result, these antibodies exhibited 10% or higher cytotoxic activity against both pancreatic cancer cell lines, whereas a cytotoxic activity less than 5% was obtained by using monoclonal antibodies reactive with the CAPRIN-1 protein itself but unreactive with the surface of cancer cells or in the absence of antibodies. These results demonstrated that the obtained anti-CAPRIN-1 monoclonal antibodies damage CAPRIN-1-expressing cancer cells through their ADCC activity. These results about cytotoxic activity were obtained by: mixing the antibody against CAPRIN-1 used in the present invention, a cell population containing human NK cells, and  $2 \times 10^3$  tumor cells with incorporated chromium 51, as described above: culturing the cells for 4 hours; after the culture, measuring the amount of chromium 51 released into the medium; and calculating the cytotoxic activity against the tumor cells according to the following equation for calculation\*:

$$\text{*Equation: Cytotoxic activity (\%)} = \frac{\text{Amount of chromium 51 released from the tumor cells supplemented with the antibody against CAPRIN-1 and a cell population containing human NK cells}}{\text{Amount of chromium 51 released from tumor cells supplemented with 1 N hydrochloric acid}} \times 100.$$

[Example 7] Antitumor effect of anti-CAPRIN-1 monoclonal antibody on mouse *in vivo*

**[0158]** Next, the obtained anti-CAPRIN-1 monoclonal antibodies (human-chicken chimeric antibody #1) were evaluated for their antitumor effects on cancer-bearing mice *in vivo*. Each antibody used was column-purified from the culture supernatant in the same way as above.

**[0159]** The monoclonal antibodies against CAPRIN-1 were studied for their antitumor effects using cancer-bearing Balb/c nude mice in which a CAPRIN-1-expressing human pancreatic cancer cell line Capan-2 was transplanted.  $5 \times 10^6$  Capan-2 cells (purchased from ATCC) per mouse were subcutaneously transplanted into the abdomens of 6 Balb/c nude mice (manufactured by Japan SLC, Inc.) and grown until the size of tumor became approximately 5 mm in diameter. Each monoclonal antibody against CAPRIN-1 was intraperitoneally administered at a dose of 200  $\mu$ g (200  $\mu$ l)/mouse to 3 of these cancer-bearing mice. Then, the antibody was intraperitoneally administered to the cancer-bearing mice at the same dose as above twice a week. The size of tumor was measured every day, and the antitumor effect was observed. On the other hand, PBS(-) was administered instead of the antibody to the remaining 3 cancer-bearing mice, which were in turn used as a control group. As a result, in the groups that received the anti-CAPRIN-1 mouse monoclonal antibodies #1 to #22, tumor was regressed to 84% (with the tumor volume in the control group defined as 100%) on day 27 after the start of antibody administration. In addition, tumor growth was reduced to 75% at day 35. The human-chicken chimeric antibodies #1, #2, and #3 were also evaluated in the same way as above. As a result, tumor growth was reduced to 80% in all the cases on day 27 after the start of antibody administration. These results demonstrated that the obtained antibodies against CAPRIN-1 exert an *in vivo* antitumor effect on CAPRIN-1-expressing human pancreatic cancer cells. The size of tumor was calculated in terms of volume according to the equation:  $0.5 \times (\text{Major axis} \times \text{Minor axis} \times \text{Minor axis})$ .

[Example 8] Identification of peptide in CAPRIN-1 protein to which anti-CAPRIN-1 antibody reactive with cancer cell surface binds

**[0160]** The cancer cell surface-reactive anti-CAPRIN-1 monoclonal antibodies #12 to #22 obtained above were used to identify partial sequences in CAPRIN-1 proteins recognized thereby.

**[0161]** First, DTT (manufactured by Sigma-Aldrich Corp./Fluka) was added at a final concentration of 10 mM to 100  $\mu$ l of a 1  $\mu$ g/ $\mu$ l solution containing recombinant CAPRIN-1 proteins dissolved in PBS, and reacted at 95°C for 5 minutes to reduce disulfide bonds in the CAPRIN-1 proteins. Next, 20 mM (final concentration) iodoacetamide (manufactured by Wako Pure Chemical Industries, Ltd.) was added thereto, followed by the alkylation reaction of thiol groups at 37°C for 30 minutes under shading conditions. 50  $\mu$ g each of the anti-CAPRIN-1 monoclonal antibodies #12 to #22 was added to 40  $\mu$ g of the obtained reduced alkylated CAPRIN-1 proteins. The total amount of each mixture was adjusted to 1 ml with a 20 mM phosphate buffer solution (pH 7.0). The resulting mixture was reacted overnight at 4°C while mixed by stirring.

**[0162]** Next, trypsin (manufactured by Promega K.K.) was added at a final concentration of 0.2  $\mu$ g to each reaction mixture and reacted at 37°C for 1 hour, 2 hours, 4 hours, and 12 hours. Then, the reaction mixture was mixed with protein A-glass beads (manufactured by GE Healthcare Bio-Sciences Ltd.) blocked with PBS containing 1% BSA (manufactured by Sigma-Aldrich Corp.) and washed with PBS in advance, 1 mM calcium carbonate, and NP-40 buffer solution (20 mM phosphate buffer solution (pH 7.4), 5 mM EDTA, 150 mM NaCl, 1% NP-40) and reacted for 30 minutes.

**[0163]** Each reaction solution was washed with a 25 mM ammonium carbonate buffer solution (pH 8.0), followed by the elution of antigen-antibody complexes using 100  $\mu$ l of 0.1 % formic acid. The eluate was analyzed by LC-MS using Q-TOF Premier (manufactured by Waters-MicroMass). This analysis followed the protocol attached to the instrument.

**[0164]** As a result, a polypeptide of SEQ ID NO: 273 was identified as a partial CAPRIN-1 sequence recognized by all of the anti-CAPRIN-1 monoclonal antibodies #12 to #22. In the polypeptide of SEQ ID NO: 273, a peptide of SEQ ID NO: 274 was identified as a partial sequence recognized by the monoclonal antibodies #13 to #16, #17 to #19, and #21. As its partial sequence peptide, a peptide of SEQ ID NO: 275 was further found to be recognized by the monoclonal antibodies #13 to #16.

**[0165]** Also, the human-chicken chimeric monoclonal antibody #1, the human-chicken chimeric monoclonal antibody #3, and the mouse monoclonal antibodies #1, #2, #3, #4, #5, #6, #7, #8, #9, #10, and #11 were used to identify epitope peptides in CAPRIN-1 proteins recognized thereby. 93 candidate peptides consisting of 12 to 16 amino acids in the amino acid sequence of the human CAPRIN-1 protein were synthesized and each dissolved at a concentration of 1 mg/ml in DMSO.

**[0166]** Each peptide was dissolved at a concentration of 30  $\mu$ g/ml in a 0.1 M sodium carbonate buffer solution (pH 9.6). The solution was added at a concentration of 100  $\mu$ l/well to a 96-well plate (manufactured by Thermo Fisher Scientific Inc./Nunc, product No.: 436006) and left standing overnight at 4°C. The solution in each well was discarded, and 10 mM ethanolamine/0.1 M sodium carbonate buffer solution (pH 9.6) was added thereto at a concentration of 200  $\mu$ l/well and left standing at room temperature for 1 hour. Then, the solution in each well was discarded, and each well was washed twice with PBS containing 0.5% Tween 20 (PBST) to prepare a peptide-immobilized plate.

**[0167]** The cell culture supernatant containing the human-chicken chimeric monoclonal antibody #1 (#1), the human-

chicken chimeric monoclonal antibody #3 (#3), or the mouse monoclonal antibody (#1, #2, #3, #4, #5, #6, #7, #8, #9, #10, or #11) was added at a concentration of 50  $\mu$ l/well to each plate thus obtained. After shaking at room temperature for 1 hour, the solution in each well was discarded, and each well was washed three times with PBST. Next, a secondary antibody solution containing HRP-labeled anti-human IgG (manufactured by Invitrogen Corp.) antibodies diluted 3000- to 4000-fold with PBST was added at a concentration of 50  $\mu$ l/well to the human-chicken chimeric monoclonal antibody wells, while a secondary antibody solution containing HRP-labeled anti-mouse IgG (manufactured by Invitrogen Corp.) antibodies diluted 3000- to 4000-fold with PBST was added at a concentration of 50  $\mu$ l/well to the mouse monoclonal antibody wells. Then, the solution in each well was discarded, and each well was washed six times with PBST.

**[0168]** A TMB substrate solution (manufactured by Thermo Fisher Scientific Inc.) was added thereto at a concentration of 100  $\mu$ l/well and left standing for 15 to 30 minutes to cause color reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at a concentration of 100  $\mu$ l/well. The absorbance was measured at 450 nm and 595 nm using an absorption spectrometer. As a result, a polypeptide of SEQ ID NO: 266 was identified as a partial CAPRIN-1 sequence recognized by all of the anti-CAPRIN-1 antibodies human-chicken chimeric monoclonal antibody #1 and anti-CAPRIN-1 monoclonal antibodies #1 to #5. In the polypeptide of SEQ ID NO: 266, a peptide of SEQ ID NO: 267 was identified as a partial sequence recognized by the human-chicken chimeric monoclonal antibody #1 and the mouse monoclonal antibodies #3 and #4. In the polypeptide of SEQ ID NO: 266, a peptide of SEQ ID NO: 268 was identified as a partial sequence recognized by the mouse monoclonal antibodies #1, #2, and #5. Thus, the polypeptide of SEQ ID NO: 266 was found to contain an epitope region for the anti-CAPRIN-1 antibodies human-chicken chimeric monoclonal antibody #1 and mouse monoclonal antibodies #1, #2, #3, #4, and #5. Also, a polypeptide comprising the amino acid sequence of SEQ ID NO: 270 was identified as a partial CAPRIN-1 sequence recognized by all of the anti-CAPRIN-1 monoclonal antibodies #6, #7, and #8. Thus, the polypeptide of SEQ ID NO: 270 was found to contain an epitope region for the anti-CAPRIN-1 antibodies #6, #7, and #8. In addition, a polypeptide comprising the amino acid sequence of SEQ ID NO: 272 was identified as a partial CAPRIN-1 sequence recognized by all of the anti-CAPRIN-1 monoclonal antibodies #9, #10, and #11. Thus, the polypeptide of SEQ ID NO: 272 was found to contain an epitope region for the anti-CAPRIN-1 antibodies #9, #10, and #11. In addition, a polypeptide comprising the amino acid sequence of SEQ ID NO: 269 was identified as a partial CAPRIN-1 sequence recognized by the human-chicken chimeric monoclonal antibody #3. Thus, the polypeptide of SEQ ID NO: 269 was found to contain an epitope region for the human-chicken chimeric monoclonal antibody #3.

#### Industrial Applicability

**[0169]** The antibody of the present invention is useful in the treatment of pancreatic cancer.

#### Free Text for Sequence Listing

**[0170]** SEQ ID NOs: 31 to 36, 130, and 257 to 262: Primers

#### SEQUENCE LISTING

**[0171]**

<110> TORAY INDUSTRIES, INC.

<120> Pharmaceutical Composition for Treatment and/or Prevention of Pancreatic Cancer

<130> PH-5298-PCT

<150> JP2011-171310

<151> 2011-08-04

<160> 275

<170> PatentIn version 3.1

<210> 1

<211> 5562

<212> DNA

# EP 2 740 489 B1

<213> Homo sapiens

<220>

<221> CDS

5 <222> (190)..(2319)

<223>

<400> 1

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|    | ctctcggtgc agcgggacag ggcgaagcgg cctgcgcca cggagcgcgc gacactgccc  | 120 |
| 15 | ggaagggacc gccacccttg cccctcagc tgccactcg tgatttccag cggcctccgc   | 180 |
|    | gcgcgcacg atg ccc tcg gcc acc agc cac agc ggg agc ggc agc aag tcg | 231 |
|    | Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser           |     |
|    | 1 5 10                                                            |     |
| 20 | tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg agt gag gcg gcc gcg   | 279 |
|    | Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala   |     |
|    | 15 20 25 30                                                       |     |
| 25 | gga gcc ggg gcc gcc gcg ccg gct tct cag cac ccc gca acc ggc acc   | 327 |
|    | Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr   |     |
|    | 35 40 45                                                          |     |
| 30 | ggc gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg atc gac   | 375 |
|    | Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp   |     |
|    | 50 55 60                                                          |     |
| 35 | aag aaa ctt cgg aac ctg gag aag aaa aag ggt aag ctt gat gat tac   | 423 |
|    | Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr   |     |
|    | 65 70 75                                                          |     |
| 40 | cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag ctg gat   | 471 |
|    | Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp   |     |
|    | 80 85 90                                                          |     |
| 45 | gcc gtt tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca aaa   | 519 |
|    | Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys   |     |
|    | 95 100 105 110                                                    |     |
| 50 | gaa tta cag agg agt ttc atg gca cta agt caa gat att cag aaa aca   | 567 |
|    | Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr   |     |
|    | 115 120 125                                                       |     |

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|    |                                                                 |      |
|----|-----------------------------------------------------------------|------|
|    | ata aag aag aca gca cgt cgg gag cag ctt atg aga gaa gaa gct gaa | 615  |
|    | Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu |      |
|    | 130 135 140                                                     |      |
| 5  | cag aaa cgt tta aaa act gta ctt gag cta cag tat gtt ttg gac aaa | 663  |
|    | Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys |      |
|    | 145 150 155                                                     |      |
| 10 | ttg gga gat gat gaa gtg cgg act gac ctg aaa caa ggt ttg aat gga | 711  |
|    | Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly |      |
|    | 160 165 170                                                     |      |
| 15 | gtg cca ata ttg tcc gaa gag gag ttg tca ttg ttg gat gaa ttc tat | 759  |
|    | Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr |      |
|    | 175 180 185 190                                                 |      |
| 20 | aag cta gta gac cct gaa cgg gac atg agc ttg agg ttg aat gaa cag | 807  |
|    | Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln |      |
|    | 195 200 205                                                     |      |
| 25 | tat gaa cat gcc tcc att cac ctg tgg gac ctg ctg gaa ggg aag gaa | 855  |
|    | Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu |      |
|    | 210 215 220                                                     |      |
| 30 | aaa cct gta tgt gga acc acc tat aaa gtt cta aag gaa att gtt gag | 903  |
|    | Lys Pro Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu |      |
|    | 225 230 235                                                     |      |
| 35 | cgt gtt ttt cag tca aac tac ttt gac agc acc cac aac cac cag aat | 951  |
|    | Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn |      |
|    | 240 245 250                                                     |      |
| 40 | ggg ctg tgt gag gaa gaa gag gca gcc tca gca cct gca gtt gaa gac | 999  |
|    | Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp |      |
|    | 255 260 265 270                                                 |      |
| 45 | cag gta cct gaa gct gaa cct gag cca gca gaa gag tac act gag caa | 1047 |
|    | Gln Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln |      |
|    | 275 280 285                                                     |      |
| 50 | agt gaa gtt gaa tca aca gag tat gta aat aga cag ttc atg gca gaa | 1095 |
|    | Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu |      |
|    | 290 295 300                                                     |      |
| 55 | aca cag ttc acc agt ggt gaa aag gag cag gta gat gag tgg aca gtt | 1143 |
|    | Thr Gln Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val |      |
|    | 305 310 315                                                     |      |
| 60 | gaa acg gtt gag gtg gta aat tca ctc cag cag caa cct cag gct gca | 1191 |
|    | Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala |      |
|    | 320 325 330                                                     |      |
| 65 | tcc cct tca gta cca gag ccc cac tct ttg act cca gtg gct cag gca | 1239 |
|    | Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala |      |
|    | 335 340 345 350                                                 |      |
| 70 | gat ccc ctt gtg aga aga cag cga gta caa gac ctt atg gca caa atg | 1287 |
|    | Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met |      |
|    | 355 360 365                                                     |      |
| 75 | cag ggt ccc tat aat ttc ata cag gat tca atg ctg gat ttt gaa aat | 1335 |
|    | Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn |      |
|    | 370 375 380                                                     |      |
| 80 | cag aca ctt gat cct gcc att gta tct gca cag cct atg aat cca aca | 1383 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr |      |
|    |     |     | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |      |
| 5  | caa | aac | atg | gac | atg | ccc | cag | ctg | gtt | tgc | cct | cca | gtt | cat | tct | gaa | 1431 |
|    | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys | Pro | Pro | Val | His | Ser | Glu |      |
|    |     | 400 |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     |      |
|    | tct | aga | ctt | gct | cag | cct | aat | caa | gtt | cct | gta | caa | cca | gaa | gcg | aca | 1479 |
|    | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr |      |
| 10 | 415 |     |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |      |
|    | cag | gtt | cct | ttg | gta | tca | tcc | aca | agt | gag | ggg | tac | aca | gca | tct | caa | 1527 |
|    | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln |      |
|    |     |     |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |      |
| 15 | ccc | ttg | tac | cag | cct | tct | cat | gct | aca | gag | caa | cga | cca | cag | aag | gaa | 1575 |
|    | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu |      |
|    |     |     |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |      |
|    | cca | att | gat | cag | att | cag | gca | aca | atc | tct | tta | aat | aca | gac | cag | act | 1623 |
|    | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr |      |
| 20 |     |     | 465 |     |     |     | 470 |     |     |     |     |     | 475 |     |     |     |      |
|    | aca | gca | tca | tca | tcc | ctt | cct | gct | gcg | tct | cag | cct | caa | gta | ttt | cag | 1671 |
|    | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln |      |
|    |     | 480 |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |      |
| 25 | gct | ggg | aca | agc | aaa | cct | tta | cat | agc | agt | gga | atc | aat | gta | aat | gca | 1719 |
|    | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala |      |
|    | 495 |     |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |      |
|    | gct | cca | ttc | caa | tcc | atg | caa | acg | gtg | ttc | aat | atg | aat | gcc | cca | gtt | 1767 |
|    | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val |      |
| 30 |     |     |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |      |
|    | cct | cct | gtt | aat | gaa | cca | gaa | act | tta | aaa | cag | caa | aat | cag | tac | cag | 1815 |
|    | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Asn | Gln | Tyr | Gln |      |
|    |     |     |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |      |
| 35 | gcc | agt | tat | aac | cag | agc | ttt | tct | agt | cag | cct | cac | caa | gta | gaa | caa | 1863 |
|    | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln |      |
|    |     |     | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |      |
|    | aca | gag | ctt | cag | caa | gaa | cag | ctt | caa | aca | gtg | gtt | ggc | act | tac | cat | 1911 |
|    | Thr | Glu | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His |      |
| 40 |     | 560 |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     |      |
|    | ggg | tcc | cca | gac | cag | tcc | cat | caa | gtg | act | ggg | aac | cac | cag | cag | cct | 1959 |
|    | Gly | Ser | Pro | Asp | Gln | Ser | His | Gln | Val | Thr | Gly | Asn | His | Gln | Gln | Pro |      |
|    | 575 |     |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |      |
| 45 | cct | cag | cag | aac | act | gga | ttt | cca | cgt | agc | aat | cag | ccc | tat | tac | aat | 2007 |
|    | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser | Asn | Gln | Pro | Tyr | Tyr | Asn |      |
|    |     |     |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |      |
|    | agt | cgt | ggg | gtg | tct | cgt | gga | ggc | tcc | cgt | ggg | gct | aga | ggc | ttg | atg | 2055 |
|    | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met |      |
| 50 |     |     |     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |      |
|    | aat | gga | tac | cgg | ggc | cct | gcc | aat | gga | ttc | aga | gga | gga | tat | gat | ggg | 2103 |
|    | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly |      |
|    |     |     | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |      |
| 55 | tac | cgc | cct | tca | ttc | tct | aac | act | cca | aac | agt | ggg | tat | aca | cag | tct | 2151 |
|    | Tyr | Arg | Pro | Ser | Phe | Ser | Asn | Thr | Pro | Asn | Ser | Gly | Tyr | Thr | Gln | Ser |      |

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|    | 640                                                                                                                                                   | 645 | 650 |      |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| 5  | cag ttc agt gct ccc cgg gat tac tct ggc tat caa cgg gat gga tat<br>Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr<br>655 660 665 670 |     |     | 2199 |
|    | cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga gcc<br>Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala<br>675 680 685     |     |     | 2247 |
| 10 | cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg caa<br>Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln<br>690 695 700     |     |     | 2295 |
| 15 | atg aac act cag caa gtg aat taa tctgattcac aggattatgt ttaatcgcca<br>Met Asn Thr Gln Gln Val Asn<br>705                                                |     |     | 2349 |
|    | aaaacacact ggccagtgtg ccataatatg ttaccagaag agttattatc tatttgttct                                                                                     |     |     | 2409 |
|    | ccctttcagc aaacttattg taaagggact gttttcatcc cataaagaca ggactacaat                                                                                     |     |     | 2469 |
| 20 | tgctcagcttt ctattacctg gatatggaag gaaactatgt ttactctgca tgttctgtcc                                                                                    |     |     | 2529 |
|    | taagcgtcat cttgagcctt gcacatgata ctacagattcc tcacccttgc ttaggagtaa                                                                                    |     |     | 2589 |
|    | aacaatatac tttacagggc gataataatc tccatagtta tttgaagtgg cttgaaaaag                                                                                     |     |     | 2649 |
| 25 | gcaagattga cttttatgac attggataaa atctacaaat cagccctcga gttattcaat                                                                                     |     |     | 2709 |
|    | gataactgac aaactaaatt atttccctag aaaggaagat gaaaggagtg gagtgtggtt                                                                                     |     |     | 2769 |
|    | tggcagaaca actgcatttc acagcttttc cagttaaatt ggagcactga acgttcagat                                                                                     |     |     | 2829 |
| 30 | gcataccaaa ttatgcatgg gtcctaatac cacatataag gctggctacc agctttgaca                                                                                     |     |     | 2889 |
|    | cagcactggt catctggcca aacaactgtg gttaaaaaca catgtaaaat gctttttaac                                                                                     |     |     | 2949 |
|    | agctgatact gtataagaca aagccaagat gcaaaattag gctttgattg gcactttttg                                                                                     |     |     | 3009 |
| 35 | aaaaatatgc aacaaatatg ggatgtaatc cggatggccg cttctgtact taatgtgaaa                                                                                     |     |     | 3069 |
|    | tatttagata cctttttgaa cacttaacag tttctttgag acaatgactt ttgtaaggat                                                                                     |     |     | 3129 |
|    | tggtagctatc tatcattcct tatgacatgt acattgtctg tcaactaatcc ttggattttg                                                                                   |     |     | 3189 |
| 40 | ctgtattgtc acctaaattg gtacaggtac tgatgaaaat ctctagtgga taatcataac                                                                                     |     |     | 3249 |
|    | actctcggtc acatgttttt ccttcagctt gaaagctttt ttttaaaagg aaaagatacc                                                                                     |     |     | 3309 |
|    | aaatgcctgc tgctaccacc cttttcaatt gctatctttt gaaaggcacc agtatgtgtt                                                                                     |     |     | 3369 |
| 45 | ttagattgat ttccctgttt cagggaaatc acggacagta gtttcagttc tgatggtata                                                                                     |     |     | 3429 |
|    | agcaaaacaa ataaaacgtt tataaaagtt gtatcttgaa aactggtgt tcaacagcta                                                                                      |     |     | 3489 |
| 50 | gcagcttatg tgattcacc catgccacgt tagtgtcaca aattttatgg tttatctcca                                                                                      |     |     | 3549 |
|    | gcaacatttc tctagtactt gcacttatta tcttttgtct aatttaacct taactgaatt                                                                                     |     |     | 3609 |
|    | ctccgtttct cctggaggca tttatattca gtgataattc cttcccttag atgcataggg                                                                                     |     |     | 3669 |
| 55 | agagtctcta aatttgatgg aaatggacac ttgagtagtg acttagcctt atgtactctg                                                                                     |     |     | 3729 |
|    | ttggaatttg tgctagcagt ttgagcacta gttctgtgtg cctaggaagt taatgctgct                                                                                     |     |     | 3789 |

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|    |                                                                    |      |
|----|--------------------------------------------------------------------|------|
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|    | taatggtatt ttctgtgcag aaatttaaatt ttattttcag catttagccc aggaattctt | 3909 |
| 5  | ccagtaggtg ctcagctatt taaaaacaaa actattctca aacattcatc attagacaac  | 3969 |
|    | tggagttttt gctggttttg taacctacca aaatggatag gctgttgaac attccacatt  | 4029 |
| 10 | caaaagtttt gtagggtggt gggaaatggg ggatcttcaa tgtttatttt aaaataaaat  | 4089 |
|    | aaaataagtt cttgactttt ctcatgtgtg gttgtggtac atcatattgg aagggttaac  | 4149 |
|    | ctgttacttt ggcaaatgag tatttttttg ctagcacctc cccttgctg ctttaaataga  | 4209 |
| 15 | catctgcctg ggatgtacca caaccatatt ttacctgtat cttaggggaa tggataaaat  | 4269 |
|    | atgtgtggtt tactgggtaa tccctagatg atgtatgctt gcagtcctat ataaaactaa  | 4329 |
|    | atgtgtatc tgtgtagaaa ataatttcat gacatttaca atcaggactg aagtaagttc   | 4389 |
| 20 | ttcacacagt gacctctgaa tcagtttcag agaagggatg ggggagaaaa tgccttctag  | 4449 |
|    | gttttgaact tctatgcatt agtgcagatg ttgtgaatgt gtaaagggtg tcatagtttg  | 4509 |
|    | actgtttcta tgtatgtttt ttcaaagaat tggttccttt tttgaactat aatttttctt  | 4569 |
| 25 | tttttggtta ttttaccatc acagttttaa tgtatatctt ttatgtctct actcagacca  | 4629 |
|    | tattttttaa ggggtgcctc attatggggc agagaacttt tcaataagtc tcattaagat  | 4689 |
| 30 | ctgaatcttg gttctaagca ttctgtataa tatgtgattg cttgtcctag ctgcagaagg  | 4749 |
|    | ccttttggtt ggtcaaatgc atatttttagc agagtttcaa ggaaatgatt gtcacacatg | 4809 |
|    | tcactgtagc ctcttggtgt agcaagctca catacaaaat acttttgtat atgcataata  | 4869 |
| 35 | taaatcatct catgtggata tgaaacttct tttttaaaac ttaaaaagggt agaatgttat | 4929 |
|    | tgattacctt gattagggca gttttatttc cagatcctaa taattcctaa aaaatatgga  | 4989 |
|    | aaagtttttt ttcaatcatt gtaccttgat attaaaacaa atatccttta agtatttcta  | 5049 |
| 40 | atcagtttagc ttctacagtt cttttgtctc cttttatatg cagctcttac gtgggagact | 5109 |
|    | tttccactta aaggagacat agaatgtgtg cttattctca gaaggttcat taactgaggt  | 5169 |
| 45 | gatgagttaa caactagttg agcagtcagc ttcctaagtg ttttaggaca tttgttcatt  | 5229 |
|    | atattttccg tcatataact agaggaagtg gaatgcagat aagtgccgaa ttcaaaccct  | 5289 |
|    | tcattttatg ttttaagctcc tgaatctgca ttccacttgg gttgttttta agcattctaa | 5349 |
| 50 | attttagttg attataagtt agatttcaca gaatcagtat tgcccttgat cttgtccttt  | 5409 |
|    | ttatggagtt aacgggggag aagaccctc aggaaaacga aagtaaattg ttaaggctca   | 5469 |
|    | tcttcatacc tttttccatt ttgaatccta caaaaatact gcaaaagact agtgaatgtt  | 5529 |
| 55 | taaaattaca ctagattaaa taatatgaaa gtc                               | 5562 |

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|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Met | Pro | Ser | Ala | Thr | Ser | His | Ser | Gly | Ser | Gly | Ser | Lys | Ser | Ser | Gly |  |
|    | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     | 15  |     |     |  |
| 5  | Pro | Pro | Pro | Pro | Ser | Gly | Ser | Ser | Gly | Ser | Glu | Ala | Ala | Ala | Gly | Ala |  |
|    |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Gly | Ala | Ala | Ala | Pro | Ala | Ser | Gln | His | Pro | Ala | Thr | Gly | Thr | Gly | Ala |  |
|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 15 | Val | Gln | Thr | Glu | Ala | Met | Lys | Gln | Ile | Leu | Gly | Val | Ile | Asp | Lys | Lys |  |
|    | 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Leu | Arg | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu |  |
|    | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 25 | Arg | Met | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val |  |
|    |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 30 | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 35 | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys |  |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| 40 | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys |  |
|    |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 45 | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly |  |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| 50 | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro |  |
|    |     |     |     | 165 |     |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| 55 | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| 60 | Val | Asp | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| 65 | His | Ala | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro |  |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 70 | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Val | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 75 | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu |  |

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|    | 245 |     |     |     |     |     |     | 250 |     |     |     |     |     |     | 255 |     |  |  |  |  |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|--|
| 5  | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Ala | Val | Glu | Asp | Gln | Val |  |  |  |  |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |  |  |  |  |
|    | Pro | Glu | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu |  |  |  |  |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |  |  |  |  |
| 10 | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln |  |  |  |  |  |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |  |  |  |  |
| 15 | Phe | Thr | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr |  |  |  |  |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |  |  |  |  |
|    | Val | Glu | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro |  |  |  |  |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |  |  |  |  |
| 20 | Ser | Val | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro |  |  |  |  |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     |     | 350 |     |  |  |  |  |  |
| 25 | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly |  |  |  |  |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |  |  |  |  |
|    | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr |  |  |  |  |  |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |  |  |  |  |
| 30 | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn |  |  |  |  |  |
|    |     | 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |  |  |  |  |
| 35 | Met | Asp | Met | Pro | Gln | Leu | Val | Cys | Pro | Pro | Val | His | Ser | Glu | Ser | Arg |  |  |  |  |  |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |  |  |  |  |
|    | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val |  |  |  |  |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |  |  |  |  |
| 40 | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu |  |  |  |  |  |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |  |  |  |  |
| 45 | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile |  |  |  |  |  |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |  |  |  |  |
|    | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala |  |  |  |  |  |
|    |     | 465 |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |  |  |  |  |
| 50 | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly |  |  |  |  |  |
|    |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |  |  |  |  |  |
| 55 | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro |  |  |  |  |  |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |  |  |  |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| 5  | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser |
|    |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| 10 | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| 15 | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser |
|    |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |
| 20 | Pro | Asp | Gln | Ser | His | Gln | Val | Thr | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln |
|    |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| 25 | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser | Asn | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg |
|    |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| 30 | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly |
|    | 610 |     |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| 35 | Tyr | Arg | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg |
|    | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| 40 | Pro | Ser | Phe | Ser | Asn | Thr | Pro | Asn | Ser | Gly | Tyr | Thr | Gln | Ser | Gln | Phe |
|    |     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |
| 45 | Ser | Ala | Pro | Arg | Asp | Tyr | Ser | Gly | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln |
|    |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |
| 50 | Asn | Phe | Lys | Arg | Gly | Ser | Gly | Gln | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg |
|    |     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| 55 | Gly | Arg | Gly | Gly | Pro | Pro | Arg | Pro | Asn | Arg | Gly | Met | Pro | Gln | Met | Asn |
|    | 690 |     |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |
| 60 | Thr | Gln | Gln | Val | Asn |     |     |     |     |     |     |     |     |     |     |     |
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|    |                                                                   |     |
|----|-------------------------------------------------------------------|-----|
|    | cagagggctg ctggctggct aagtcctcc cgctcccggc tctcgctca ctaggagcgg   | 60  |
|    | ctctcgggtgc agcgggacag ggcgaagcgg cctgcgcca cggagcgcgc gacactgccc | 120 |
| 5  | ggaagggacc gccacccttg cccctcagc tgccactcg tgatttccag cggcctcgc    | 180 |
|    | gcgcgcacg atg ccc tcg gcc acc agc cac agc ggg agc ggc agc aag tcg | 231 |
|    | Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser           |     |
|    | 1 5 10                                                            |     |
| 10 | tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg agt gag gcg gcc gcg   | 279 |
|    | Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala   |     |
|    | 15 20 25 30                                                       |     |
|    | gga gcc ggg gcc gcc gcg ccg gct tct cag cac ccc gca acc ggc acc   | 327 |
| 15 | Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr   |     |
|    | 35 40 45                                                          |     |
|    | ggc gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg atc gac   | 375 |
|    | Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp   |     |
|    | 50 55 60                                                          |     |
| 20 | aag aaa ctt cgg aac ctg gag aag aaa aag ggt aag ctt gat gat tac   | 423 |
|    | Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr   |     |
|    | 65 70 75                                                          |     |
|    | cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag ctg gat   | 471 |
| 25 | Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp   |     |
|    | 80 85 90                                                          |     |
|    | gcc gtt tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca aaa   | 519 |
|    | Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys   |     |
|    | 95 100 105 110                                                    |     |
| 30 | gaa tta cag agg agt ttc atg gca cta agt caa gat att cag aaa aca   | 567 |
|    | Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr   |     |
|    | 115 120 125                                                       |     |
|    | ata aag aag aca gca cgt ccg gag cag ctt atg aga gaa gaa gct gaa   | 615 |
| 35 | Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu   |     |
|    | 130 135 140                                                       |     |
|    | cag aaa cgt tta aaa act gta ctt gag cta cag tat gtt ttg gac aaa   | 663 |
|    | Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys   |     |
|    | 145 150 155                                                       |     |
| 40 | ttg gga gat gat gaa gtg ccg act gac ctg aaa caa ggt ttg aat gga   | 711 |
|    | Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly   |     |
|    | 160 165 170                                                       |     |
| 45 | gtg cca ata ttg tcc gaa gag gag ttg tca ttg ttg gat gaa ttc tat   | 759 |
|    | Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr   |     |
|    | 175 180 185 190                                                   |     |
|    | aag cta gta gac cct gaa ccg gac atg agc ttg agg ttg aat gaa cag   | 807 |
| 50 | Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln   |     |
|    | 195 200 205                                                       |     |
|    | tat gaa cat gcc tcc att cac ctg tgg gac ctg ctg gaa ggg aag gaa   | 855 |
|    | Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu   |     |
|    | 210 215 220                                                       |     |
| 55 | aaa cct gta tgt gga acc acc tat aaa gtt cta aag gaa att gtt gag   | 903 |
|    | Lys Pro Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu   |     |
|    | 225 230 235                                                       |     |

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|    |                                                                 |      |
|----|-----------------------------------------------------------------|------|
|    | cgt gtt ttt cag tca aac tac ttt gac agc acc cac aac cac cag aat | 951  |
|    | Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn |      |
|    | 240 245 250                                                     |      |
| 5  | ggg ctg tgt gag gaa gaa gag gca gcc tca gca cct gca gtt gaa gac | 999  |
|    | Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp |      |
|    | 255 260 265 270                                                 |      |
| 10 | cag gta cct gaa gct gaa cct gag cca gca gaa gag tac act gag caa | 1047 |
|    | Gln Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln |      |
|    | 275 280 285                                                     |      |
| 15 | agt gaa gtt gaa tca aca gag tat gta aat aga cag ttc atg gca gaa | 1095 |
|    | Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu |      |
|    | 290 295 300                                                     |      |
| 20 | aca cag ttc acc agt ggt gaa aag gag cag gta gat gag tgg aca gtt | 1143 |
|    | Thr Gln Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val |      |
|    | 305 310 315                                                     |      |
| 25 | gaa acg gtt gag gtg gta aat tca ctc cag cag caa cct cag gct gca | 1191 |
|    | Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala |      |
|    | 320 325 330                                                     |      |
| 30 | tcc cct tca gta cca gag ccc cac tct ttg act cca gtg gct cag gca | 1239 |
|    | Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala |      |
|    | 335 340 345 350                                                 |      |
| 35 | gat ccc ctt gtg aga aga cag cga gta caa gac ctt atg gca caa atg | 1287 |
|    | Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met |      |
|    | 355 360 365                                                     |      |
| 40 | cag ggt ccc tat aat ttc ata cag gat tca atg ctg gat ttt gaa aat | 1335 |
|    | Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn |      |
|    | 370 375 380                                                     |      |
| 45 | cag aca ctt gat cct gcc att gta tct gca cag cct atg aat cca aca | 1383 |
|    | Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr |      |
|    | 385 390 395                                                     |      |
| 50 | caa aac atg gac atg ccc cag ctg gtt tgc cct cca gtt cat tct gaa | 1431 |
|    | Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu |      |
|    | 400 405 410                                                     |      |
| 55 | tct aga ctt gct cag cct aat caa gtt cct gta caa cca gaa gcg aca | 1479 |
|    | Ser Arg Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr |      |
|    | 415 420 425 430                                                 |      |
| 60 | cag gtt cct ttg gta tca tcc aca agt gag ggg tac aca gca tct caa | 1527 |
|    | Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln |      |
|    | 435 440 445                                                     |      |
| 65 | ccc ttg tac cag cct tct cat gct aca gag caa cga cca cag aag gaa | 1575 |
|    | Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu |      |
|    | 450 455 460                                                     |      |
| 70 | cca att gat cag att cag gca aca atc tct tta aat aca gac cag act | 1623 |
|    | Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr |      |
|    | 465 470 475                                                     |      |
| 75 | aca gca tca tca tcc ctt cct gct gcg tct cag cct caa gta ttt cag | 1671 |
|    | Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln |      |
|    | 480 485 490                                                     |      |

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|    |  |                                                                    |      |
|----|--|--------------------------------------------------------------------|------|
|    |  | gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta aat gca    | 1719 |
|    |  | Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala    |      |
|    |  | 495 500 505 510                                                    |      |
| 5  |  | gct cca ttc caa tcc atg caa acg gtg ttc aat atg aat gcc cca gtt    | 1767 |
|    |  | Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val    |      |
|    |  | 515 520 525                                                        |      |
| 10 |  | cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag tac cag    | 1815 |
|    |  | Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln    |      |
|    |  | 530 535 540                                                        |      |
|    |  | gcc agt tat aac cag agc ttt tct agt cag cct cac caa gta gaa caa    | 1863 |
|    |  | Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln    |      |
|    |  | 545 550 555                                                        |      |
| 15 |  | aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act tac cat    | 1911 |
|    |  | Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His    |      |
|    |  | 560 565 570                                                        |      |
| 20 |  | ggc tcc cca gac cag tcc cat caa gtg act ggt aac cac cag cag cct    | 1959 |
|    |  | Gly Ser Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro    |      |
|    |  | 575 580 585 590                                                    |      |
|    |  | cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat tac aat    | 2007 |
|    |  | Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn    |      |
|    |  | 595 600 605                                                        |      |
| 25 |  | agt cgt ggt gtg tct cgt gga ggc tcc cgt ggt gct aga ggc ttg atg    | 2055 |
|    |  | Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met    |      |
|    |  | 610 615 620                                                        |      |
| 30 |  | aat gga tac cgg ggc cct gcc aat gga ttc aga gga gga tat gat ggt    | 2103 |
|    |  | Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly    |      |
|    |  | 625 630 635                                                        |      |
| 35 |  | tac cgc cct tca ttc tct aac act cca aac agt ggt tat aca cag tct    | 2151 |
|    |  | Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser    |      |
|    |  | 640 645 650                                                        |      |
|    |  | cag ttc agt gct ccc cgg gat tac tct ggc tat caa cgg gat gga tat    | 2199 |
|    |  | Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr    |      |
|    |  | 655 660 665 670                                                    |      |
| 40 |  | cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga gcc    | 2247 |
|    |  | Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala    |      |
|    |  | 675 680 685                                                        |      |
| 45 |  | cca cga ggt aat att ttg tgg tgg tga tcctagctcc taagtggagc          | 2294 |
|    |  | Pro Arg Gly Asn Ile Leu Trp Trp                                    |      |
|    |  | 690                                                                |      |
| 50 |  | ttctgttctg gccttggaag agctgttaat agtctgcatg ttaggaatac atttatcctt  | 2354 |
|    |  | tccagacttg ttgctaggga tttaatgaaa tgctctgttt ctaaaactta atcttgacc   | 2414 |
|    |  | caaattttaa tttttgaatg atttaatttt ccctgttact atataaactg tcttgaaaac  | 2474 |
|    |  | tagaacatat tctcttctca gaaaaagtgt ttttccaact gaaaattatt tttcaggtcc  | 2534 |
|    |  | taaaacctgc taaatgtttt taggaagtac ttactgaaac atttttgtaa gacatttttg  | 2594 |
| 55 |  | gaatgagatt gaacatttat ataaatttat tttcctctt tcattttttt gaaacatgcc   | 2654 |
|    |  | tatttatattt tagggccaga caccctttta tggccggata agccatagtt aacatttaga | 2714 |

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|    |                                                                     |      |
|----|---------------------------------------------------------------------|------|
|    | gaaccattta gaagtgatag aactaatgga atttgcaatg ccttttggac ctctattagt   | 2774 |
|    | gatataaata tcaagttatt tctgactttt aaacaaaact cccaaattcc taacttattg   | 2834 |
| 5  | agctatactt aaaaaaaatt acaggtttag agagtttttt gtttttcttt tactgttgga   | 2894 |
|    | aaactacttc ccattttggc aggaagttaa cctatttaac aattagagct agcatttcac   | 2954 |
| 10 | gtagtctgaa attcctaaatg gttctctgat ttgagggagg ttaaacaatca aacaggtttc | 3014 |
|    | ctctattggc cataacatgt ataaaatgtg tgttaaggag gaattacaac gtactttgat   | 3074 |
|    | ttgaataacta gtagaaaactg gccaggaaaa aggtacattt ttctaaaaat taatggatca | 3134 |
| 15 | cttggggaatt actgacttga ctagaagtat caaaggatgt ttgcatgtga atgtgggtta  | 3194 |
|    | tgttctttcc caccttgtag catattcgat gaaagttgag ttaactgata gctaaaaatc   | 3254 |
|    | tgttttaaca gcatgtaaaa agttatttta tctgttaaaa gtcattatac agttttgaat   | 3314 |
| 20 | gttatgtagt ttctttttta cagtttaggt aataaggtct gttttcattc tgggtgctttt  | 3374 |
|    | attaattttg atagtatgat gttacttact actgaaatgt aagctagagt gtacactaga   | 3434 |
|    | atgtaagctc catgagagca ggtaccttgt ctgtcttctc tgctgtatct attcccaacg   | 3494 |
| 25 | cttgatgatg gtgcctggca catagtaggc actcaataaa tatttggtga atgaatgaa    | 3553 |

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 <212> PRT  
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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Met | Pro | Ser | Ala | Thr | Ser | His | Ser | Gly | Ser | Gly | Ser | Lys | Ser | Ser | Gly |  |
|    | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 5  | Pro | Pro | Pro | Pro | Ser | Gly | Ser | Ser | Gly | Ser | Glu | Ala | Ala | Ala | Gly | Ala |  |
|    |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Gly | Ala | Ala | Ala | Pro | Ala | Ser | Gln | His | Pro | Ala | Thr | Gly | Thr | Gly | Ala |  |
|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 15 | Val | Gln | Thr | Glu | Ala | Met | Lys | Gln | Ile | Leu | Gly | Val | Ile | Asp | Lys | Lys |  |
|    |     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Leu | Arg | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu |  |
|    | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 25 | Arg | Met | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val |  |
|    |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 30 | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 35 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 40 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 50 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 55 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |

# EP 2 740 489 B1

|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| 5  | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys |
|    |     |     | 130 |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
|    | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly |
| 10 | 145 |     |     |     |     | 150 |     |     |     | 155 |     |     |     |     |     | 160 |
|    | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| 15 | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
|    | Val | Asp | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu |
| 20 |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
|    | His | Ala | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| 25 | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Val | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
|    | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu |
| 30 |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
|    | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Ala | Val | Glu | Asp | Gln | Val |
|    |     |     |     | 260 |     |     |     | 265 |     |     |     |     |     | 270 |     |     |
| 35 | Pro | Glu | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
|    | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln |
| 40 |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
|    | Phe | Thr | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr |
|    | 305 |     |     |     |     | 310 |     |     |     | 315 |     |     |     |     |     | 320 |
| 45 | Val | Glu | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
|    | Ser | Val | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro |
| 50 |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
|    | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| 55 | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr |

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[illegible]

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Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser Gln Phe  
645 650 655

5 Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln  
660 665 670

10 Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg  
675 680 685

Gly Asn Ile Leu Trp Trp  
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|    |                                                                  |     |
|----|------------------------------------------------------------------|-----|
|    | gtcacaata acttgagatt tgcaaaagaa ttacagagga gtttc atg gca tta agt | 57  |
|    | Met Ala Leu Ser                                                  |     |
|    | 1                                                                |     |
| 5  | caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt  | 105 |
|    | Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu  |     |
|    | 5 10 15 20                                                       |     |
| 10 | atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc  | 153 |
|    | Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu  |     |
|    | 25 30 35                                                         |     |
| 15 | cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg  | 201 |
|    | Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu  |     |
|    | 40 45 50                                                         |     |
| 20 | aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg  | 249 |
|    | Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser  |     |
|    | 55 60 65                                                         |     |
| 25 | ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc  | 297 |
|    | Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser  |     |
|    | 70 75 80                                                         |     |
| 30 | ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac  | 345 |
|    | Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp  |     |
|    | 85 90 95 100                                                     |     |
| 35 | ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca  | 393 |
|    | Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala  |     |
|    | 105 110 115                                                      |     |
| 40 | cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc  | 441 |
|    | Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser  |     |
|    | 120 125 130                                                      |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | act | cac | aac | cac | cag | aat | ggg | cta | tgt | gag | gaa | gaa | gag | gca | gcc | tca | 489  |
|    | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |      |
|    |     |     | 135 |     |     |     |     | 140 |     |     |     |     |     | 145 |     |     |      |
| 5  | gca | cct | aca | gtt | gaa | gac | cag | gta | gct | gaa | gct | gag | cct | gag | cca | gca | 537  |
|    | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |      |
|    |     |     | 150 |     |     |     | 155 |     |     |     |     |     | 160 |     |     |     |      |
| 10 | gaa | gaa | tac | act | gaa | caa | agt | gaa | gtt | gaa | tca | aca | gag | tat | gta | aat | 585  |
|    | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |      |
|    | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     | 180 |      |
|    | aga | caa | ttt | atg | gca | gaa | aca | cag | ttc | agc | agt | ggg | gaa | aag | gag | cag | 633  |
|    | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln |      |
|    |     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |     | 195 |     |      |
| 15 | gta | gat | gag | tgg | acg | gtc | gaa | aca | gtg | gag | gtg | gtg | aat | tca | ctc | cag | 681  |
|    | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |      |
|    |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     | 210 |     |     |      |
| 20 | cag | caa | cct | cag | gct | gcg | tct | cct | tca | gta | cca | gag | ccc | cac | tct | ttg | 729  |
|    | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu |      |
|    |     |     | 215 |     |     |     |     | 220 |     |     |     |     | 225 |     |     |     |      |
|    | act | ccg | gtg | gct | cag | gca | gat | ccc | ctt | gtg | aga | aga | cag | cga | gtc | cag | 777  |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |      |
|    |     |     | 230 |     |     |     | 235 |     |     |     |     |     | 240 |     |     |     |      |
| 25 | gac | ctt | atg | gcg | cag | atg | cag | ggg | ccc | tat | aat | ttc | ata | cag | gat | tca | 825  |
|    | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |      |
|    | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |     |     |     | 260 |      |
| 30 | atg | ctg | gat | ttt | gaa | aac | cag | aca | ctc | gat | cct | gcc | att | gta | tct | gca | 873  |
|    | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |      |
|    |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |     | 275 |     |      |
|    | cag | cct | atg | aat | ccg | aca | caa | aac | atg | gac | atg | ccc | cag | ctg | gtt | tgc | 921  |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |      |
|    |     |     |     | 280 |     |     |     |     | 285 |     |     |     |     | 290 |     |     |      |
| 35 | cct | cca | gtt | cat | tct | gaa | tct | aga | ctt | gct | caa | cct | aat | caa | gtt | cct | 969  |
|    | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |      |
|    |     |     | 295 |     |     |     |     | 300 |     |     |     |     | 305 |     |     |     |      |
| 40 | gta | caa | cca | gaa | gct | aca | cag | gtt | cct | ttg | gtt | tca | tcc | aca | agt | gag | 1017 |
|    | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |      |
|    |     |     | 310 |     |     |     | 315 |     |     |     |     | 320 |     |     |     |     |      |
| 45 | ggg | tat | aca | gca | tct | caa | ccc | ttg | tac | cag | cct | tct | cat | gct | aca | gag | 1065 |
|    | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |      |
|    | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |     |     |     | 340 |      |
|    | caa | cga | cca | caa | aag | gaa | cca | att | gac | cag | att | cag | gca | aca | atc | tct | 1113 |
|    | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser |      |
|    |     |     |     |     | 345 |     |     |     | 350 |     |     |     |     | 355 |     |     |      |
| 50 | tta | aat | aca | gac | cag | act | aca | gcg | tca | tca | tcc | ctt | ccg | gct | gct | tct | 1161 |
|    | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser |      |
|    |     |     |     | 360 |     |     |     | 365 |     |     |     |     |     | 370 |     |     |      |
| 55 | cag | cct | cag | gta | ttc | cag | gct | ggg | aca | agc | aaa | cca | tta | cat | agc | agt | 1209 |
|    | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser |      |
|    |     |     | 375 |     |     |     |     | 380 |     |     |     |     | 385 |     |     |     |      |
|    | gga | atc | aat | gta | aat | gca | gct | cca | ttc | caa | tcc | atg | caa | acg | gtg | ttc | 1257 |

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|    | Gly                    | Ile        | Asn        | Val         | Asn        | Ala          | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr        | Val | Phe |      |
|----|------------------------|------------|------------|-------------|------------|--------------|-----|-----|-----|-----|-----|-----|-----|------------|-----|-----|------|
|    | 390                    |            |            |             |            |              | 395 |     |     |     |     | 400 |     |            |     |     |      |
| 5  | aat                    | atg        | aat        | gcc         | cca        | gtt          | cct | cct | gtt | aat | gaa | cca | gaa | act        | ttg | aaa | 1305 |
|    | Asn                    | Met        | Asn        | Ala         | Pro        | Val          | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr        | Leu | Lys |      |
|    | 405                    |            |            |             |            | 410          |     |     |     | 415 |     |     |     |            |     | 420 |      |
|    | caa                    | caa        | aat        | cag         | tac        | cag          | gcc | agt | tat | aac | cag | agc | ttt | tct        | agt | cag | 1353 |
| 10 | Gln                    | Gln        | Asn        | Gln         | Tyr        | Gln          | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser        | Ser | Gln |      |
|    |                        |            |            | 425         |            |              |     |     | 430 |     |     |     |     |            | 435 |     |      |
|    | cct                    | cac        | caa        | gta         | gaa        | caa          | aca | gag | gga | tgc | cgc | aaa | tga | acactcagca |     |     | 1402 |
|    | Pro                    | His        | Gln        | Val         | Glu        | Gln          | Thr | Glu | Gly | Cys | Arg | Lys |     |            |     |     |      |
|    |                        |            |            | 440         |            |              |     | 445 |     |     |     |     |     |            |     |     |      |
| 15 | agtgaattaa             | tctgattcac | aggattatgt | ttaaacgccca | aaaacacact | ggccagtgtgta |     |     |     |     |     |     |     |            |     |     | 1462 |
|    | ccataaatatg            | ttaccagaag | agttattatc | tatttggttct | ccctttcagg | aaacttattg   |     |     |     |     |     |     |     |            |     |     | 1522 |
|    | taaagggact             | gttttcatcc | cataaagaca | ggactacaat  | tgtcagcttt | atattacctg   |     |     |     |     |     |     |     |            |     |     | 1582 |
| 20 | gaaaaaaaaa             | aaaaaaaaaa | aaa        |             |            |              |     |     |     |     |     |     |     |            |     |     | 1605 |
|    | <210> 6                |            |            |             |            |              |     |     |     |     |     |     |     |            |     |     |      |
|    | <211> 448              |            |            |             |            |              |     |     |     |     |     |     |     |            |     |     |      |
| 25 | <212> PRT              |            |            |             |            |              |     |     |     |     |     |     |     |            |     |     |      |
|    | <213> Canis familiaris |            |            |             |            |              |     |     |     |     |     |     |     |            |     |     |      |
|    | <400> 6                |            |            |             |            |              |     |     |     |     |     |     |     |            |     |     |      |

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|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr | Ala | Arg |
|    | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| 5  | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu | Lys | Thr |
|    |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| 10 | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val |
|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| 15 | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu |
|    |     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| 20 | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu |
|    | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| 25 | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile |
|    |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| 30 | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| 35 | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| 40 | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu |
|    |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | 145 | 150 | 155 |     | 160 |
| 5  | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr |     | 165 | 170 |     | 175 |
| 10 | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly |     | 180 | 185 |     | 190 |
|    | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val |     | 195 | 200 |     | 205 |
| 15 | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | 210 | 215 |     | 220 |     |
| 20 | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | 225 | 230 | 235 |     | 240 |
|    | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe |     | 245 | 250 |     | 255 |
| 25 | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala |     | 260 | 265 |     | 270 |
| 30 | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro |     | 275 | 280 |     | 285 |
|    | Gln | Leu | Val | Cys | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | 290 | 295 |     | 300 |     |
| 35 | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | 305 | 310 | 315 |     | 320 |
| 40 | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser |     | 325 | 330 |     | 335 |
| 45 | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln |     | 340 | 345 |     | 350 |
|    | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu |     | 355 | 360 |     | 365 |
| 50 | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | 370 | 375 |     | 380 |     |
| 55 | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | 385 | 390 | 395 |     | 400 |

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Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro  
405 410 415

5 Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser  
420 425 430

10 Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Gly Cys Arg Lys  
435 440 445

<210> 7

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<220>

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20 <223>

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|    |                                                                 |     |
|----|-----------------------------------------------------------------|-----|
|    | atg ccg tcg gcc acc agc ctc agc gga agc ggc agc aag tcg tcg ggc | 48  |
|    | Met Pro Ser Ala Thr Ser Leu Ser Gly Ser Gly Ser Lys Ser Ser Gly |     |
|    | 1 5 10 15                                                       |     |
| 5  | ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg | 96  |
|    | Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala |     |
|    | 20 25 30                                                        |     |
| 10 | ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag | 144 |
|    | Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln |     |
|    | 35 40 45                                                        |     |
| 15 | cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag | 192 |
|    | His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln |     |
|    | 50 55 60                                                        |     |
| 20 | atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag | 240 |
|    | Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys |     |
|    | 65 70 75 80                                                     |     |
| 25 | ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt | 288 |
|    | Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu |     |
|    | 85 90 95                                                        |     |
| 30 | aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat | 336 |
|    | Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn |     |
|    | 100 105 110                                                     |     |
| 35 | aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt | 384 |
|    | Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser |     |
|    | 115 120 125                                                     |     |
| 40 | caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt | 432 |
|    | Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu |     |
|    | 130 135 140                                                     |     |
| 45 | atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc | 480 |
|    | Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu |     |
|    | 145 150 155 160                                                 |     |
| 50 | cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg | 528 |
| 55 |                                                                 |     |

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|    |     |     |     |      |     |     |     |     |     |     |     |     |     |     |      |     |      |
|----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|------|
|    | Gln | Tyr | Val | Leu  | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val | Arg | Thr | Asp  | Leu |      |
|    |     |     |     |      | 165 |     |     |     |     | 170 |     |     |     |     | 175  |     |      |
| 5  | aag | caa | ggt | ttg  | aat | gga | gtg | cca | ata | ttg | tct | gaa | gaa | gaa | ttg  | tcg | 576  |
|    | Lys | Gln | Gly | Leu  | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu  | Ser |      |
|    |     |     |     | 180  |     |     |     |     | 185 |     |     |     |     | 190 |      |     |      |
| 10 | ttg | ttg | gat | gaa  | ttc | tac | aaa | tta | gca | gac | cct | gaa | cgg | gac | atg  | agc | 624  |
|    | Leu | Leu | Asp | Glu  | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met  | Ser |      |
|    |     |     | 195 |      |     |     |     | 200 |     |     |     |     | 205 |     |      |     |      |
|    | ttg | agg | ttg | aat  | gag | cag | tat | gaa | cat | gct | tcc | att | cac | ctg | tggt | gac | 672  |
|    | Leu | Arg | Leu | Asn  | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp  | Asp |      |
|    |     | 210 |     |      |     |     | 215 |     |     |     |     | 220 |     |     |      |     |      |
| 15 | ttg | ctg | gaa | gga  | aag | gaa | aag | tct | gta | tgt | gga | aca | acc | tat | aaa  | gca | 720  |
|    | Leu | Leu | Glu | Gly  | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys  | Ala |      |
|    |     | 225 |     |      |     | 230 |     |     |     |     | 235 |     |     |     |      | 240 |      |
| 20 | cta | aag | gaa | att  | gtt | gag | cgt | gtt | ttc | cag | tca | aat | tac | ttt | gac  | agc | 768  |
|    | Leu | Lys | Glu | Ile  | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp  | Ser |      |
|    |     |     |     |      | 245 |     |     |     |     | 250 |     |     |     |     | 255  |     |      |
|    | act | cac | aac | cac  | cag | aat | ggg | cta | tgt | gag | gaa | gaa | gag | gca | gcc  | tca | 816  |
|    | Thr | His | Asn | His  | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala  | Ser |      |
|    |     |     |     | 260  |     |     |     |     | 265 |     |     |     |     | 270 |      |     |      |
| 25 | gca | cct | aca | gtt  | gaa | gac | cag | gta | gct | gaa | gct | gag | cct | gag | cca  | gca | 864  |
|    | Ala | Pro | Thr | Val  | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro  | Ala |      |
|    |     |     | 275 |      |     |     |     | 280 |     |     |     |     | 285 |     |      |     |      |
| 30 | gaa | gaa | tac | act  | gaa | caa | agt | gaa | gtt | gaa | tca | aca | gag | tat | gta  | aat | 912  |
|    | Glu | Glu | Tyr | Thr  | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val  | Asn |      |
|    |     |     | 290 |      |     |     | 295 |     |     |     |     | 300 |     |     |      |     |      |
|    | aga | caa | ttt | atg  | gca | gaa | aca | cag | ttc | agc | agt | ggg | gaa | aag | gag  | cag | 960  |
|    | Arg | Gln | Phe | Met  | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu  | Gln |      |
|    |     | 305 |     |      |     | 310 |     |     |     |     | 315 |     |     |     |      | 320 |      |
| 35 | gta | gat | gag | tggt | acg | gtc | gaa | aca | gtg | gag | gtg | gtg | aat | tca | ctc  | cag | 1008 |
|    | Val | Asp | Glu | Trp  | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu  | Gln |      |
|    |     |     |     |      | 325 |     |     |     |     | 330 |     |     |     |     | 335  |     |      |
| 40 | cag | caa | cct | cag  | gct | gcg | tct | cct | tca | gta | cca | gag | ccc | cac | tct  | ttg | 1056 |
|    | Gln | Gln | Pro | Gln  | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser  | Leu |      |
|    |     |     |     | 340  |     |     |     |     | 345 |     |     |     |     | 350 |      |     |      |
|    | act | ccg | gtg | gct  | cag | gca | gat | ccc | ctt | gtg | aga | aga | cag | cga | gtc  | cag | 1104 |
|    | Thr | Pro | Val | Ala  | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val  | Gln |      |
|    |     |     | 355 |      |     |     |     | 360 |     |     |     |     | 365 |     |      |     |      |
| 45 | gac | ctt | atg | gcg  | cag | atg | cag | ggg | ccc | tat | aat | ttc | ata | cag | gat  | tca | 1152 |
|    | Asp | Leu | Met | Ala  | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp  | Ser |      |
|    |     |     | 370 |      |     |     | 375 |     |     |     |     | 380 |     |     |      |     |      |
| 50 | atg | ctg | gat | ttt  | gaa | aac | cag | aca | ctc | gat | cct | gcc | att | gta | tct  | gca | 1200 |
|    | Met | Leu | Asp | Phe  | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser  | Ala |      |
|    |     |     | 385 |      |     | 390 |     |     |     |     | 395 |     |     |     |      | 400 |      |
|    | cag | cct | atg | aat  | ccg | aca | caa | aac | atg | gac | atg | ccc | cag | ctg | gtt  | tgc | 1248 |
|    | Gln | Pro | Met | Asn  | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val  | Cys |      |
|    |     |     |     |      | 405 |     |     |     |     | 410 |     |     |     |     | 415  |     |      |
| 55 | cct | cca | gtt | cat  | tct | gaa | tct | aga | ctt | gct | caa | cct | aat | caa | gtt  | cct | 1296 |
|    | Pro | Pro | Val | His  | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val  | Pro |      |

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|    | 420                                                                                                                                                   | 425  | 430 |  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----|--|
| 5  | gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag<br>Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu<br>435 440 445     | 1344 |     |  |
| 10 | ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag<br>Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu<br>450 455 460     | 1392 |     |  |
| 15 | caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct<br>Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser<br>465 470 475 480 | 1440 |     |  |
| 20 | tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct<br>Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser<br>485 490 495     | 1488 |     |  |
| 25 | cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt<br>Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser<br>500 505 510     | 1536 |     |  |
| 30 | gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc<br>Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe<br>515 520 525     | 1584 |     |  |
| 35 | aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa<br>Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys<br>530 535 540     | 1632 |     |  |
| 40 | caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag<br>Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln<br>545 550 555 560 | 1680 |     |  |
| 45 | cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca<br>Pro His Gln Val Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr<br>565 570 575         | 1728 |     |  |
| 50 | gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act<br>Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr<br>580 585 590     | 1776 |     |  |
| 55 | ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc<br>Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser<br>595 600 605     | 1824 |     |  |
| 60 | agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt<br>Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg<br>610 615 620     | 1872 |     |  |
| 65 | ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc<br>Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe<br>625 630 635 640 | 1920 |     |  |
| 70 | aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac<br>Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn<br>645 650 655     | 1968 |     |  |
| 75 | agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc<br>Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly<br>660 665 670     | 2016 |     |  |
| 80 | tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag<br>Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln<br>675 680 685     | 2064 |     |  |

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|    |                                                                      |      |
|----|----------------------------------------------------------------------|------|
|    | agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc      | 2112 |
|    | Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro      |      |
|    | 690 695 700                                                          |      |
| 5  | aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa              | 2154 |
|    | Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn                  |      |
|    | 705 710 715                                                          |      |
|    | tctgattcac aggattatgt ttaaacgccca aaaacacact ggccagtgtgta ccataatatg | 2214 |
| 10 | ttaccagaag agttattatc tatttggttct ccctttcagg aaacttattg taaagggact   | 2274 |
|    | gttttcatcc cataaagaca ggactacaat tgtcagcttt atattacctg gatatggaag    | 2334 |
|    | gaaactatctt ttattctgca tgttcttctc aagcgtcatc ttgagccttg cacatgatac   | 2394 |
| 15 | tcagattcct cacccttgct taggagtaaa acataatata ctttacaggg tgatatctcc    | 2454 |
|    | atagttatctt gaagtggctt ggaaaaagca agattaactt ctgacattgg ataaaaatca   | 2514 |
|    | acaaatcagc cctagagtta ttcaaagtgt aattgacaaa aactaaaata tttcccttcg    | 2574 |
| 20 | agaaggagtg gaatgtggtt tggcagaaca actgcatttc acagcttttc cggttaaatt    | 2634 |
|    | ggagcactaa acgttttagat gcataccaaa ttatgcatgg gcccttaata taaaaggctg   | 2694 |
|    | gctaccagct ttgacacagc actattcatc ctctggccaa acaactgtgg ttaaacaaca    | 2754 |
| 25 | catgtaaat gctttttaac agctgatact ataataagac aaagccaaaa tgcaaaaatt     | 2814 |
|    | gggctttgat tggcactttt tgaaaaatat gcaacaaata tgggatgtaa tctggatggc    | 2874 |
| 30 | cgcttctgta cttaatgtga agtatttaga tacctttttg aacacttaac agtttcttct    | 2934 |
|    | gacaatgact tttgtaagga ttggtactat ctatcattcc ttataatgta cattgtctgt    | 2994 |
|    | cactaatcct cagatcttgc tgtattgtca cctaaattgg tacaggtagt gatgaaaata    | 3054 |
| 35 | tctaattgat aatcataaca ctcttggtca catgtttttc ctgcagcctg aagggtttta    | 3114 |
|    | aaagaaaaag atatcaaatg cctgctgcta ccaccctttt aaattgctat cttttgaaaa    | 3174 |
|    | gcaccagtat gtgttttaga ttgatttccc tattttaggg aaatgacaga cagtagtttc    | 3234 |
| 40 | agttctgatg gtataagcaa aacaaataaa acatgtttat aaaagttgta tcttgaaaca    | 3294 |
|    | ctgggtgttca acagctagca gcttatgtgg ttcaccccat gcattgttag tgtttcagat   | 3354 |
|    | tttatgggta tctccagcag ctgtttctgt agtacttgca tttatctttt gtctaaccct    | 3414 |
| 45 | aatattctca cggaggcatt tatattcaaa gtggatgatcc cttcacttag acgcataggg   | 3474 |
|    | agagtcacaa gtttgatgaa gaggacagtg tagtaattta tatgctgttg gaatttgtgc    | 3534 |
|    | tagcagtttg agcactagtt ctgtgtgcct atgaacttaa tgctgcttgt catattccac    | 3594 |
| 50 | tttgacttca tggagaatta atcccatcta ctcagcaaag gctatactaa tactaagtta    | 3654 |
|    | atggatattt ctgtgcagaa attgaatttt gttttattag catttagcta aggaattttt    | 3714 |
| 55 | ccagtaggtg ctgagctact aaagaaaaac aaaaacaaga cacaaaacta ttctcaaaca    | 3774 |
|    | ttcattgtta gacaactgga gtttttgctg gttttgtaac ctactaaaat ggataggctg    | 3834 |

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|    |                                                                    |      |
|----|--------------------------------------------------------------------|------|
|    | ttgaacattc cacattcaaa agttttttgt aggggtggtgg ggaagggggg gtgtcttcaa | 3894 |
|    | tgtttatttt aaaataaaat aagttcttga cttttctcat gtgtggttgt ggtacatcat  | 3954 |
| 5  | attggaaggg ttatctgttt acttttgcaa atgagtattt ctcttgctag cacctcccgt  | 4014 |
|    | tgtgcgcttt aaatgacatc tgcctgggat gtaccacaac catatgttag ctgtatttta  | 4074 |
| 10 | tggggaatag ataaaatatt cgtggtttat tgggtaatcc ctagatgtgt atgcttacia  | 4134 |
|    | tcctatatat aaaactaaat                                              | 4154 |

|    |                        |
|----|------------------------|
|    | <210> 8                |
|    | <211> 717              |
| 15 | <212> PRT              |
|    | <213> Canis familiaris |
|    | <400> 8                |

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

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 5  | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp |  |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 10 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 15 | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser |  |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 20 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 25 | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |  |
|    | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| 30 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 35 | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
| 40 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |  |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |  |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |  |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| 50 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 55 | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |  |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |  |
|    | 450 |     |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| 5  | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
|    | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser |  |
| 10 |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
|    | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser |  |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |
| 15 | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe |  |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
|    | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys |  |
| 20 |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |
|    | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln |  |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |
| 25 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Pro | His | Gln | Val | Glu | Gln | Thr | Asp | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr |  |
|    |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |
|    | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp | Gln | Pro | His | Gln | Val | Thr |  |
| 30 |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |
|    | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser |  |
| 35 |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
|    | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg |  |
|    | 610 |     |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |
| 40 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly | Phe |  |
|    | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |  |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser | Phe | Ser | Asn | Thr | Pro | Asn |  |
|    |     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |  |
|    | Ser | Gly | Tyr | Thr | Gln | Ser | Gln | Phe | Ser | Ala | Pro | Arg | Asp | Tyr | Ser | Gly |  |
| 50 |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |  |
|    | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln | Asn | Phe | Lys | Arg | Gly | Ser | Gly | Gln |  |
|    |     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |  |
| 55 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg | Gly | Arg | Gly | Gly | Pro | Pro | Arg | Pro |  |
|    | 690 |     |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |  |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Arg | Gly | Met | Pro | Gln | Met | Asn | Thr | Gln | Gln | Val | Asn |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |

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|    |                                                                 |     |
|----|-----------------------------------------------------------------|-----|
|    | atg ccg tcg gcc acc agc ctc agc gga agc ggc agc aag tcg tcg ggc | 48  |
|    | Met Pro Ser Ala Thr Ser Leu Ser Gly Ser Gly Ser Lys Ser Ser Gly |     |
|    | 1 5 10 15                                                       |     |
| 5  | ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg | 96  |
|    | Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala |     |
|    | 20 25 30                                                        |     |
| 10 | ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag | 144 |
|    | Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln |     |
|    | 35 40 45                                                        |     |
| 15 | cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag | 192 |
|    | His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln |     |
|    | 50 55 60                                                        |     |
| 20 | atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag | 240 |
|    | Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys |     |
|    | 65 70 75 80                                                     |     |
| 25 | ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt | 288 |
|    | Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu |     |
|    | 85 90 95                                                        |     |
| 30 | aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat | 336 |
|    | Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn |     |
|    | 100 105 110                                                     |     |
| 35 | aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt | 384 |
|    | Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser |     |
|    | 115 120 125                                                     |     |
| 40 | caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt | 432 |
|    | Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu |     |
|    | 130 135 140                                                     |     |
| 45 | atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc | 480 |
|    | Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu |     |
|    | 145 150 155 160                                                 |     |
| 50 | cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg | 528 |
|    | Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu |     |
|    | 165 170 175                                                     |     |
| 55 | aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg | 576 |
|    | Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser |     |
|    | 180 185 190                                                     |     |
| 60 | ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc | 624 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser |      |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |      |
| 5  | ttg | agg | ttg | aat | gag | cag | tat | gaa | cat | gct | tcc | att | cac | ctg | tgg | gac | 672  |
|    | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp |      |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |      |
| 10 | ttg | ctg | gaa | gga | aag | gaa | aag | tct | gta | tgt | gga | aca | acc | tat | aaa | gca | 720  |
|    | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala |      |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |      |
| 15 | cta | aag | gaa | att | gtt | gag | cgt | gtt | ttc | cag | tca | aat | tac | ttt | gac | agc | 768  |
|    | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser |      |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |      |
| 20 | act | cac | aac | cac | cag | aat | ggg | cta | tgt | gag | gaa | gaa | gag | gca | gcc | tca | 816  |
|    | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |      |
|    |     |     |     | 260 |     |     |     | 265 |     |     |     |     |     | 270 |     |     |      |
| 25 | gca | cct | aca | gtt | gaa | gac | cag | gta | gct | gaa | gct | gag | cct | gag | cca | gca | 864  |
|    | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |      |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |      |
| 30 | gaa | gaa | tac | act | gaa | caa | agt | gaa | gtt | gaa | tca | aca | gag | tat | gta | aat | 912  |
|    | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |      |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |      |
| 35 | aga | caa | ttt | atg | gca | gaa | aca | cag | ttc | agc | agt | ggg | gaa | aag | gag | cag | 960  |
|    | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln |      |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |      |
| 40 | gta | gat | gag | tgg | acg | gtc | gaa | aca | gtg | gag | gtg | gtg | aat | tca | ctc | cag | 1008 |
|    | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |      |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |      |
| 45 | cag | caa | cct | cag | gct | gcg | tct | cct | tca | gta | cca | gag | ccc | cac | tct | ttg | 1056 |
|    | Gln | Gln | Pro | Gln | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | Pro | His | Ser | Leu |      |
|    |     |     |     | 340 |     |     |     | 345 |     |     |     |     |     | 350 |     |     |      |
| 50 | act | ccg | gtg | gct | cag | gca | gat | ccc | ctt | gtg | aga | aga | cag | cga | gtc | cag | 1104 |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |      |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |      |
| 55 | gac | ctt | atg | gcg | cag | atg | cag | ggg | ccc | tat | aat | ttc | ata | cag | gat | tca | 1152 |
|    | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |      |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |      |
| 60 | atg | ctg | gat | ttt | gaa | aac | cag | aca | ctc | gat | cct | gcc | att | gta | tct | gca | 1200 |
|    | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |      |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |      |
| 65 | cag | cct | atg | aat | ccg | aca | caa | aac | atg | gac | atg | ccc | cag | ctg | gtt | tgc | 1248 |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |      |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |      |
| 70 | cct | cca | gtt | cat | tct | gaa | tct | aga | ctt | gct | caa | cct | aat | caa | gtt | cct | 1296 |
|    | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |      |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |      |
| 75 | gta | caa | cca | gaa | gct | aca | cag | gtt | cct | ttg | gtt | tca | tcc | aca | agt | gag | 1344 |
|    | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |      |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |      |
| 80 | ggg | tat | aca | gca | tct | caa | ccc | ttg | tac | cag | cct | tct | cat | gct | aca | gag | 1392 |
|    | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |      |

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|    | 450                                                                                                                                                   | 455          | 460 |  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-----|--|
| 5  | caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct<br>Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser<br>465 470 475 480 | 1440         |     |  |
|    | tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct<br>Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser<br>485 490 495     | 1488         |     |  |
| 10 | cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt<br>Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser<br>500 505 510     | 1536         |     |  |
| 15 | gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc<br>Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe<br>515 520 525     | 1584         |     |  |
|    | aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa<br>Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys<br>530 535 540     | 1632         |     |  |
| 20 | caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag<br>Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln<br>545 550 555 560 | 1680         |     |  |
| 25 | cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca<br>Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr<br>565 570 575     | 1728         |     |  |
|    | gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act<br>Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr<br>580 585 590     | 1776         |     |  |
| 30 | ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc<br>Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser<br>595 600 605     | 1824         |     |  |
| 35 | agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt<br>Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg<br>610 615 620     | 1872         |     |  |
| 40 | ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc<br>Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe<br>625 630 635 640 | 1920         |     |  |
|    | aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac<br>Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn<br>645 650 655     | 1968         |     |  |
| 45 | agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc<br>Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly<br>660 665 670     | 2016         |     |  |
| 50 | tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag<br>Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln<br>675 680 685     | 2064         |     |  |
|    | agt gga cca cgg gga gcc cca cga ggt aat att ttg tgg tgg tga<br>Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn Ile Leu Trp Trp<br>690 695 700                 | 2109         |     |  |
| 55 | tcctagctcc taagtggagc ttctgttctg gccttggaag agctgttcca tagtctgcat<br>gtaggttaca tgttaggaat acatttatca ttaccagact tggtgctagg gattaaatga                | 2169<br>2229 |     |  |

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|    |            |             |            |             |             |             |      |
|----|------------|-------------|------------|-------------|-------------|-------------|------|
|    | aatgctctgt | ttctaaaact  | tctcttgaac | ccaaatttaa  | ttttttgaat  | gactttccct  | 2289 |
|    | gttactatat | aaattgtctt  | gaaaactaga | acattttctcc | tcctcagaaa  | aagtgttttt  | 2349 |
| 5  | ccaactgcaa | attatttttc  | aggtcctaaa | acctgctaaa  | tgttttttagg | aagtacttac  | 2409 |
|    | tgaaacattt | ttgtaagaca  | tttttggaat | gagattgaac  | atttatataa  | atttattatt  | 2469 |
|    | attcctcttt | cattttttgaa | catgcatatt | atatttttagg | gtcagaaatc  | ctttaatggc  | 2529 |
| 10 | caaataagcc | atagttacat  | ttagagaacc | atttagaagt  | gatagaacta  | actgaaattt  | 2589 |
|    | caatgccttt | ggatcattaa  | tagcgatata | aatttcaa    | tgtttctgac  | ttttaaataa  | 2649 |
|    | aacatccaaa | atcctaacta  | acttcctgaa | ctatatttta  | aaattacagg  | tttaaggagt  | 2709 |
| 15 | ttctgggttt | ttttctctta  | ccataggaaa | actgtttcct  | gtttggccag  | gaagtcaacc  | 2769 |
|    | tgtgtaataa | ttagaagtag  | catttcatat | gatctgaagt  | tctaaatgg   | tctctgattt  | 2829 |
|    | aagggaagtt | aaattgaata  | ggtttcctct | agttattggc  | cataacatgt  | ataaaatgta  | 2889 |
| 20 | tattaaggag | gaatacaaa   | tactttgatt | tcaatgctag  | tagaaactgg  | ccagcaaaaa  | 2949 |
|    | ggtgcatttt | atttttta    | taatggatca | cttggaatt   | actgacttga  | agtatcaaag  | 3009 |
| 25 | gatatttgca | tgtgaatgtg  | ggttatgttc | tttctcacct  | tgtagcatat  | tctatgaaag  | 3069 |
|    | ttgagttgac | tggtagctaa  | aaatctgttt | taacagcatg  | taaaaagtta  | ttttatctgt  | 3129 |
|    | tacaagtc   | tatacaattt  | tgaatgttat | gtagtttctt  | tttaacagtt  | taggtaacaa  | 3189 |
| 30 | ggtctgtttt | tcattctgg   | gcttttatta | attttgatag  | tatgatgtta  | cttactactg  | 3249 |
|    | aaatgtaagc | tagagtgtac  | actagaatgt | aagctccatg  | agagcaggta  | ccttgtctgt  | 3309 |
|    | cttcactgct | gtatctat    | ccaacgcctg | atgacagtgc  | ctgacacata  | gtaggcactc  | 3369 |
| 35 | aataaatact | tgttgaatga  | atgaatgaat | gagtactgg   | ggaatactcc  | attagctcta  | 3429 |
|    | ctcttctttt | agctagagaa  | catgagcaaa | tttgcgcatg  | acaacttcca  | ggacaggtga  | 3489 |
|    | acactgaaga | attgacctct  | taaaccta   | aatgtggtga  | caagctgccc  | acatgcttct  | 3549 |
| 40 | tgacttcaga | tgaaaatctg  | cttgaaggca | aagcaaataa  | tatttgaaag  | aaaaacccaa  | 3609 |
|    | tgccattttt | gtcttctagg  | tcgtggagg  | cccccaagac  | ccaacagagg  | gatgccgcaa  | 3669 |
|    | atgaacactc | agcaagtga   | ttaatctgat | tcacaggatt  | atgtttaaac  | gccaaaaaca  | 3729 |
| 45 | cactggccag | tgtaccataa  | tatgttacca | gaagagttat  | tatctatttg  | ttctcccttt  | 3789 |
|    | caggaaactt | attgtaaagg  | gactgttttc | atcccataaa  | gacaggacta  | caattgtcag  | 3849 |
|    | ctttatatta | cctggatatg  | gaaggaaact | atttttattc  | tgcattgttct | tcctaagcgt  | 3909 |
| 50 | catcttgagc | cttgccatg   | atactcagat | tcctcaccct  | tgcttaggag  | taaaacataa  | 3969 |
|    | tacactttac | agggtgat    | ctccatagtt | atttgaagt   | gcttggaata  | agcaagatta  | 4029 |
| 55 | acttctgaca | ttggataaaa  | atcaacaa   | cagccctaga  | gttattcaaa  | tggttaattga | 4089 |
|    | caaaaactaa | aatatttccc  | ttcgagaagg | agtggaatgt  | ggtttggcag  | aacaactgca  | 4149 |

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|    |                                                                     |      |
|----|---------------------------------------------------------------------|------|
|    | tttcacagct tttccggtta aattggagca ctaaacgttt agatgcatac caaattatgc   | 4209 |
|    | atggggccctt aatataaaaag gctggctacc agctttgaca cagcactatt catcctctgg | 4269 |
| 5  | ccaaacaact gtggttaaac aacacatgta aattgctttt taacagctga tactataata   | 4329 |
|    | agacaaagcc aaaatgcaaa aattgggctt tgattggcac tttttgaaaa atatgcaaca   | 4389 |
|    | aatatgggat gtaatctgga tggccgcttc tgtacttaat gtgaagtatt tagatacctt   | 4449 |
| 10 | tttgaacact taacagtttc ttctgacaat gacttttgta aggattggta ctatctatca   | 4509 |
|    | ttccttataa tgtacattgt ctgtcactaa tcctcagatc ttgctgtatt gtcacctaaa   | 4569 |
|    | ttggtacagg tactgatgaa aatatctaataa ggataatcat aacactcttg gtcacatggt | 4629 |
| 15 | tttcctgcag cctgaagggtt tttaaaagaa aaagatatca aatgcctgct gctaccaccc  | 4689 |
|    | ttttaaattg ctatcttttg aaaagcacca gtatgtgttt tagattgatt tccctatttt   | 4749 |
| 20 | agggaaatga cagacagtag tttcagttct gatggataaa gcaaaacaaa taaaacatgt   | 4809 |
|    | ttataaaaagt tgtatcttga aacactggtg ttcaacagct agcagcttat gtgggttcacc | 4869 |
|    | ccatgcattg ttagtggttc agattttatg gttatctcca gcagctgttt ctgtagtact   | 4929 |
| 25 | tgcatttatc                                                          | 4939 |

|    |                        |
|----|------------------------|
|    | <210> 10               |
|    | <211> 702              |
| 30 | <212> PRT              |
|    | <213> Canis familiaris |
|    | <400> 10               |

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

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|    | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5  | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu |
|    | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
|    | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |
| 10 | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| 15 | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
|    | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| 20 | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| 25 | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
|    | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| 30 | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| 35 | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
|    | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |
| 40 |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
|    | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| 45 | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
|    | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu |
| 50 |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| 55 | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |
|    | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala | 385 |     | 390 |     | 395 |     | 400 |
| 5  | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |     | 405 |     | 410 |     | 415 |     |
| 10 | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |     | 420 |     | 425 |     | 430 |     |
|    | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |     | 435 |     | 440 |     | 445 |     |
| 15 | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |     | 450 |     | 455 |     | 460 |     |
| 20 | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser |     | 465 |     | 470 |     | 475 |     |
|    | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser |     | 485 |     | 490 |     | 495 |     |
| 25 | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser |     | 500 |     | 505 |     | 510 |     |
| 30 | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe |     | 515 |     | 520 |     | 525 |     |
| 35 | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys |     | 530 |     | 535 |     | 540 |     |
|    | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln |     | 545 |     | 550 |     | 555 |     |
| 40 | Pro | His | Gln | Val | Glu | Gln | Thr | Asp | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr |     | 565 |     | 570 |     | 575 |     |
| 45 | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp | Gln | Pro | His | Gln | Val | Thr |     | 580 |     | 585 |     | 590 |     |
|    | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser |     | 595 |     | 600 |     | 605 |     |
| 50 | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg |     | 610 |     | 615 |     | 620 |     |
| 55 | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly | Phe |     | 625 |     | 630 |     | 635 |     |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn  
645 650 655

5 Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly  
660 665 670

10 Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln  
675 680 685

15 Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn Ile Leu Trp Trp  
690 695 700

<210> 11

<211> 3306

<212> DNA

<213> Canis familiaris

<220>

<221> CDS

<222> (1)..(2040)

<223>

<400> 11

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

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu |      |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |      |
| 5  | cag | tat | gtt | ttg | gac | aaa | ttg | gga | gat | gat | gaa | gtg | aga | act | gac | ctg | 528  |
|    | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu |      |
|    |     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |      |
| 10 | aag | caa | ggt | ttg | aat | gga | gtg | cca | ata | ttg | tct | gaa | gaa | gaa | ttg | tcg | 576  |
|    | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser |      |
|    |     |     |     | 180 |     |     |     | 185 |     |     |     |     |     | 190 |     |     |      |
| 15 | ttg | ttg | gat | gaa | ttc | tac | aaa | tta | gca | gac | cct | gaa | cgg | gac | atg | agc | 624  |
|    | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser |      |
|    |     |     | 195 |     |     |     | 200 |     |     |     |     | 205 |     |     |     |     |      |
| 20 | ttg | agg | ttg | aat | gag | cag | tat | gaa | cat | gct | tcc | att | cac | ctg | tgg | gac | 672  |
|    | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp |      |
|    | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |     |      |
| 25 | ttg | ctg | gaa | gga | aag | gaa | aag | tct | gta | tgt | gga | aca | acc | tat | aaa | gca | 720  |
|    | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala |      |
|    | 225 |     |     |     | 230 |     |     | 235 |     |     |     |     |     |     | 240 |     |      |
| 30 | cta | aag | gaa | att | gtt | gag | cgt | gtt | ttc | cag | tca | aat | tac | ttt | gac | agc | 768  |
|    | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser |      |
|    |     |     |     | 245 |     |     |     | 250 |     |     |     |     |     |     | 255 |     |      |
| 35 | act | cac | aac | cac | cag | aat | ggg | cta | tgt | gag | gaa | gaa | gag | gca | gcc | tca | 816  |
|    | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |      |
|    |     |     |     | 260 |     |     | 265 |     |     |     |     |     |     | 270 |     |     |      |
| 40 | gca | cct | aca | gtt | gaa | gac | cag | gta | gct | gaa | gct | gag | cct | gag | cca | gca | 864  |
|    | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |      |
|    |     |     | 275 |     |     |     | 280 |     |     |     |     |     | 285 |     |     |     |      |
| 45 | gaa | gaa | tac | act | gaa | caa | agt | gaa | gtt | gaa | tca | aca | gag | tat | gta | aat | 912  |
|    | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |      |
|    | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |     |      |
| 50 | aga | caa | ttt | atg | gca | gaa | aca | cag | ttc | agc | agt | ggt | gaa | aag | gag | cag | 960  |
|    | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln |      |
|    | 305 |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     |     | 320 |      |
| 55 | gta | gat | gag | tgg | acg | gtc | gaa | aca | gtg | gag | gtg | gtg | aat | tca | ctc | cag | 1008 |
|    | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |      |
|    |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     |     | 335 |     |      |
| 60 | cag | caa | cct | cag | gct | gcg | tct | cct | tca | gta | cca | gag | ccc | cac | tct | ttg | 1056 |
|    | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu |      |
|    |     |     | 340 |     |     |     | 345 |     |     |     |     |     |     | 350 |     |     |      |
| 65 | act | ccg | gtg | gct | cag | gca | gat | ccc | ctt | gtg | aga | aga | cag | cga | gtc | cag | 1104 |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |      |
|    |     |     | 355 |     |     |     | 360 |     |     |     |     |     | 365 |     |     |     |      |
| 70 | gac | ctt | atg | gcg | cag | atg | cag | ggg | ccc | tat | aat | ttc | ata | cag | gat | tca | 1152 |
|    | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |      |
|    |     | 370 |     |     |     | 375 |     |     |     |     |     | 380 |     |     |     |     |      |
| 75 | atg | ctg | gat | ttt | gaa | aac | cag | aca | ctc | gat | cct | gcc | att | gta | tct | gca | 1200 |
|    | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |      |
|    | 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     |     | 400 |      |
| 80 | cag | cct | atg | aat | ccg | aca | caa | aac | atg | gac | atg | ccc | cag | ctg | gtt | tgc | 1248 |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |      |

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|    |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |  |  |
|----|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|--|--|
|    | 405               |                   |                   |                   |                   |                   |                   |                   | 410               |                   |                   |                   |                   | 415               |                   |                   |      |  |  |
| 5  | cct<br>Pro        | cca<br>Pro        | gtt<br>Val        | cat<br>His<br>420 | tct<br>Ser        | gaa<br>Glu        | tct<br>Ser        | aga<br>Arg        | ctt<br>Leu<br>425 | gct<br>Ala        | caa<br>Gln        | cct<br>Pro        | aat<br>Asn        | caa<br>Gln<br>430 | gtt<br>Val        | cct<br>Pro        | 1296 |  |  |
|    | gta<br>Val        | caa<br>Gln        | cca<br>Pro<br>435 | gaa<br>Glu        | gct<br>Ala        | aca<br>Thr        | cag<br>Gln        | gtt<br>Val<br>440 | cct<br>Pro        | ttg<br>Leu        | gtt<br>Val        | tca<br>Ser        | tcc<br>Ser<br>445 | aca<br>Thr        | agt<br>Ser        | gag<br>Glu        | 1344 |  |  |
| 10 | ggg<br>Gly        | tat<br>Tyr        | aca<br>Thr<br>450 | gca<br>Ala        | tct<br>Ser        | caa<br>Gln        | ccc<br>Pro<br>455 | ttg<br>Leu        | tac<br>Tyr        | cag<br>Gln        | cct<br>Pro        | tct<br>Ser<br>460 | cat<br>His        | gct<br>Ala        | aca<br>Thr        | gag<br>Glu        | 1392 |  |  |
| 15 | caa<br>Gln<br>465 | cga<br>Arg        | cca<br>Pro        | caa<br>Gln        | aag<br>Lys        | gaa<br>Glu<br>470 | cca<br>Pro        | att<br>Ile        | gac<br>Asp        | cag<br>Gln        | att<br>Ile<br>475 | cag<br>Gln        | gca<br>Ala        | aca<br>Thr        | atc<br>Ile        | tct<br>Ser<br>480 | 1440 |  |  |
|    | tta<br>Leu        | aat<br>Asn        | aca<br>Thr        | gac<br>Asp        | cag<br>Gln<br>485 | act<br>Thr        | aca<br>Thr        | gcg<br>Ala        | tca<br>Ser<br>490 | tca<br>Ser        | tcc<br>Ser        | ctt<br>Leu        | ccg<br>Pro        | gct<br>Ala        | gct<br>Ala<br>495 | tct<br>Ser        | 1488 |  |  |
| 20 | cag<br>Gln        | cct<br>Pro        | cag<br>Gln<br>500 | gta<br>Val        | ttc<br>Phe        | cag<br>Gln        | gct<br>Ala        | ggg<br>Gly        | aca<br>Thr<br>505 | agc<br>Ser        | aaa<br>Lys        | cca<br>Pro        | tta<br>Leu        | cat<br>His<br>510 | agc<br>Ser        | agt<br>Ser        | 1536 |  |  |
| 25 | gga<br>Gly        | atc<br>Ile        | aat<br>Asn<br>515 | gta<br>Val        | aat<br>Asn        | gca<br>Ala        | gct<br>Ala        | cca<br>Pro<br>520 | ttc<br>Phe        | caa<br>Gln        | tcc<br>Ser        | atg<br>Met        | caa<br>Gln<br>525 | acg<br>Thr        | gtg<br>Val        | ttc<br>Phe        | 1584 |  |  |
|    | aat<br>Asn<br>530 | atg<br>Met        | aat<br>Asn        | gcc<br>Ala        | cca<br>Pro        | gtt<br>Val        | cct<br>Pro<br>535 | cct<br>Pro        | gtt<br>Val        | aat<br>Asn        | gaa<br>Glu<br>540 | cca<br>Pro        | gaa<br>Glu        | act<br>Thr        | ttg<br>Leu        | aaa<br>Lys        | 1632 |  |  |
| 30 | caa<br>Gln<br>545 | caa<br>Gln        | aat<br>Asn        | cag<br>Gln        | tac<br>Tyr        | cag<br>Gln<br>550 | gcc<br>Ala        | agt<br>Ser        | tat<br>Tyr        | aac<br>Asn        | cag<br>Gln<br>555 | agc<br>Ser        | ttt<br>Phe        | tct<br>Ser        | agt<br>Ser<br>560 | cag<br>Gln        | 1680 |  |  |
| 35 | cct<br>Pro        | cac<br>His        | caa<br>Gln        | gta<br>Val<br>565 | gaa<br>Glu        | caa<br>Gln        | aca<br>Thr        | gac<br>Asp        | ctt<br>Leu<br>570 | cag<br>Gln        | caa<br>Gln        | gaa<br>Glu        | cag<br>Gln        | ctt<br>Leu        | caa<br>Gln<br>575 | aca<br>Thr        | 1728 |  |  |
|    | gtg<br>Val        | gtt<br>Val        | ggc<br>Gly        | act<br>Thr<br>580 | tac<br>Tyr        | cat<br>His        | ggt<br>Gly        | tcc<br>Ser        | cag<br>Gln<br>585 | gac<br>Asp        | cag<br>Gln        | ccc<br>Pro        | cac<br>His        | caa<br>Gln<br>590 | gtg<br>Val        | act<br>Thr        | 1776 |  |  |
| 40 | ggt<br>Gly        | aac<br>Asn        | cat<br>His<br>595 | cag<br>Gln        | cag<br>Gln        | cct<br>Pro        | ccc<br>Pro        | cag<br>Gln<br>600 | cag<br>Gln        | aac<br>Asn        | act<br>Thr        | gga<br>Gly        | ttt<br>Phe<br>605 | cca<br>Pro        | cgt<br>Arg        | agc<br>Ser        | 1824 |  |  |
| 45 | agt<br>Ser        | cag<br>Gln<br>610 | ccc<br>Pro        | tat<br>Tyr        | tac<br>Tyr        | aat<br>Asn        | agt<br>Ser<br>615 | cgt<br>Arg        | ggt<br>Gly        | gtg<br>Val        | tct<br>Ser        | cgt<br>Arg<br>620 | ggt<br>Gly        | ggt<br>Gly        | tcc<br>Ser        | cgt<br>Arg        | 1872 |  |  |
|    | ggt<br>Gly<br>625 | gct<br>Ala        | aga<br>Arg        | ggc<br>Gly        | tta<br>Leu        | atg<br>Met<br>630 | aat<br>Asn        | gga<br>Gly        | tac<br>Tyr        | agg<br>Arg        | ggc<br>Gly<br>635 | cct<br>Pro        | gcc<br>Ala        | aat<br>Asn        | gga<br>Gly<br>640 | ttc<br>Phe        | 1920 |  |  |
| 50 | aga<br>Arg        | gga<br>Gly        | gga<br>Gly        | tat<br>Tyr<br>645 | gat<br>Asp        | ggt<br>Gly        | tac<br>Tyr        | cgc<br>Arg        | cct<br>Pro        | tca<br>Ser<br>650 | ttc<br>Phe        | tct<br>Ser        | aac<br>Asn        | act<br>Thr        | cca<br>Pro<br>655 | aac<br>Asn        | 1968 |  |  |
| 55 | agt<br>Ser        | ggt<br>Gly        | tat<br>Tyr<br>660 | aca<br>Thr        | cag<br>Gln        | tct<br>Ser        | cag<br>Gln        | ttc<br>Phe<br>665 | agt<br>Ser<br>665 | gct<br>Ala        | ccc<br>Pro        | cgg<br>Arg        | gac<br>Asp<br>670 | tac<br>Tyr        | tct<br>Ser        | ggc<br>Gly        | 2016 |  |  |

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tat cag cgg gga tgc cgc aaa tga acactcagca agtgaattaa tctgattcac 2070  
Tyr Gln Arg Gly Cys Arg Lys  
675

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55

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5 Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala  
 20 25 30

10 Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln  
 35 40 45

15

20

25

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | His | Pro | Ala | Thr | Gly | Thr | Gly | Ala | Val | Gln | Thr | Glu | Ala | Met | Lys | Gln |  |
|    | 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 5  | Ile | Leu | Gly | Val | Ile | Asp | Lys | Lys | Leu | Arg | Asn | Leu | Glu | Lys | Lys | Lys |  |
|    | 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     |     | 80  |  |
|    | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu | Arg | Met | Asn | Lys | Gly | Glu | Arg | Leu |  |
| 10 |     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
|    | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 15 | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser |  |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
|    | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu |  |
| 20 |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
|    | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu |  |
| 25 |     | 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
|    | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu |  |
|    |     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |  |
| 30 | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |  |
|    | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser |  |
| 35 |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
|    | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp |  |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 40 | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala |  |
|    |     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
|    | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser |  |
| 45 |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
|    | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |  |
| 50 |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
|    | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 55 | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |  |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln | 305 | 310 | 315 | 320 |
| 5  | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |     | 325 | 330 | 335 |
| 10 | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu |     | 340 | 345 | 350 |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |     | 355 | 360 | 365 |
| 15 | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |     | 370 | 375 | 380 |
| 20 | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |     | 385 | 390 | 395 |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |     | 405 | 410 | 415 |
| 25 | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |     | 420 | 425 | 430 |
| 30 | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |     | 435 | 440 | 445 |
| 35 | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |     | 450 | 455 | 460 |
|    | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser |     | 465 | 470 | 475 |
| 40 | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser |     | 485 | 490 | 495 |
| 45 | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser |     | 500 | 505 | 510 |
| 50 | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe |     | 515 | 520 | 525 |
|    | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys |     | 530 | 535 | 540 |
| 55 | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln |     | 545 | 550 | 555 |
|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     | 560 |

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|    |                                                                                                                   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-------------------------------------------------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Pro                                                                                                               | His | Gln | Val | Glu | Gln | Thr | Asp | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr |  |
|    |                                                                                                                   |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |
| 5  | Val                                                                                                               | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp | Gln | Pro | His | Gln | Val | Thr |  |
|    |                                                                                                                   |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |
| 10 | Gly                                                                                                               | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser |  |
|    |                                                                                                                   |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
| 15 | Ser                                                                                                               | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg |  |
|    |                                                                                                                   | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |
| 20 | Gly                                                                                                               | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly | Phe |  |
|    | 625                                                                                                               |     |     |     | 630 |     |     |     |     |     | 635 |     |     |     |     | 640 |  |
| 25 | Arg                                                                                                               | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser | Phe | Ser | Asn | Thr | Pro | Asn |  |
|    |                                                                                                                   |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |  |
| 30 | Ser                                                                                                               | Gly | Tyr | Thr | Gln | Ser | Gln | Phe | Ser | Ala | Pro | Arg | Asp | Tyr | Ser | Gly |  |
|    |                                                                                                                   |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |  |
| 35 | Tyr                                                                                                               | Gln | Arg | Gly | Cys | Arg | Lys |     |     |     |     |     |     |     |     |     |  |
|    |                                                                                                                   |     |     | 675 |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 40 | <210> 13<br><211> 2281<br><212> DNA<br><213> Canis familiaris<br><220><br><221> CDS<br><222> (1)..(2154)<br><223> |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 | <400> 13                                                                                                          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |

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|    |                                                                 |     |
|----|-----------------------------------------------------------------|-----|
|    | atg ccg tcg gcc acc agc ctc agc gga agc ggc agc aag tcg tcg ggc | 48  |
|    | Met Pro Ser Ala Thr Ser Leu Ser Gly Ser Gly Ser Lys Ser Ser Gly |     |
|    | 1 5 10 15                                                       |     |
| 5  | ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg | 96  |
|    | Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala |     |
|    | 20 25 30                                                        |     |
| 10 | ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag | 144 |
|    | Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln |     |
|    | 35 40 45                                                        |     |
| 15 | cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag | 192 |
|    | His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln |     |
|    | 50 55 60                                                        |     |
| 20 | atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag | 240 |
|    | Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys |     |
|    | 65 70 75 80                                                     |     |
| 25 | ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt | 288 |
|    | Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu |     |

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|    | 85                                                                                                                                                    | 90 | 95 |      |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|------|
| 5  | aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat<br>Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn<br>100 105 110     |    |    | 336  |
|    | aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt<br>Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser<br>115 120 125     |    |    | 384  |
| 10 | caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt<br>Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu<br>130 135 140     |    |    | 432  |
| 15 | atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc<br>Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu<br>145 150 155 160 |    |    | 480  |
|    | cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg<br>Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu<br>165 170 175     |    |    | 528  |
| 20 | aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg<br>Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser<br>180 185 190     |    |    | 576  |
| 25 | ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc<br>Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser<br>195 200 205     |    |    | 624  |
|    | ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac<br>Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp<br>210 215 220     |    |    | 672  |
| 30 | ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca<br>Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala<br>225 230 235 240 |    |    | 720  |
| 35 | cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc<br>Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser<br>245 250 255     |    |    | 768  |
|    | act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca<br>Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser<br>260 265 270     |    |    | 816  |
| 40 | gca cct aca gtt gaa gac cag gta gct gaa gct gag cct gag cca gca<br>Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala<br>275 280 285     |    |    | 864  |
| 45 | gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat gta aat<br>Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn<br>290 295 300     |    |    | 912  |
|    | aga caa ttt atg gca gaa aca cag ttc agc agt ggt gaa aag gag cag<br>Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln<br>305 310 315 320 |    |    | 960  |
| 50 | gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag<br>Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln<br>325 330 335     |    |    | 1008 |
| 55 | cag caa cct cag gct gcg tct cct tca gta cca gag ccc cac tct ttg<br>Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu<br>340 345 350     |    |    | 1056 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | act | ccg | gtg | gct | cag | gca | gat | ccc | ctt | gtg | aga | aga | cag | cga | gtc | cag | 1104 |
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |      |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |      |
| 5  | gac | ctt | atg | gcg | cag | atg | cag | ggg | ccc | tat | aat | ttc | ata | cag | gat | tca | 1152 |
|    | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |      |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |      |
|    | atg | ctg | gat | ttt | gaa | aac | cag | aca | ctc | gat | cct | gcc | att | gta | tct | gca | 1200 |
| 10 | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |      |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |      |
|    | cag | cct | atg | aat | ccg | aca | caa | aac | atg | gac | atg | ccc | cag | ctg | gtt | tgc | 1248 |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |      |
|    |     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |      |
| 15 | cct | cca | gtt | cat | tct | gaa | tct | aga | ctt | gct | caa | cct | aat | caa | gtt | cct | 1296 |
|    | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |      |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |      |
|    | gta | caa | cca | gaa | gct | aca | cag | gtt | cct | ttg | gtt | tca | tcc | aca | agt | gag | 1344 |
| 20 | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |      |
|    |     |     | 435 |     |     |     | 440 |     |     |     |     |     | 445 |     |     |     |      |
|    | ggg | tat | aca | gca | tct | caa | ccc | ttg | tac | cag | cct | tct | cat | gct | aca | gag | 1392 |
| 25 | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |      |
|    |     | 450 |     |     |     | 455 |     |     |     |     |     | 460 |     |     |     |     |      |
|    | caa | cga | cca | caa | aag | gaa | cca | att | gac | cag | att | cag | gca | aca | atc | tct | 1440 |
|    | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser |      |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |      |
| 30 | tta | aat | aca | gac | cag | act | aca | gcg | tca | tca | tcc | ctt | ccg | gct | gct | tct | 1488 |
|    | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser |      |
|    |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |     | 495 |     |      |
|    | cag | cct | cag | gta | ttc | cag | gct | ggg | aca | agc | aaa | cca | tta | cat | agc | agt | 1536 |
| 35 | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser |      |
|    |     |     |     | 500 |     |     |     | 505 |     |     |     |     |     | 510 |     |     |      |
|    | gga | atc | aat | gta | aat | gca | gct | cca | ttc | caa | tcc | atg | caa | acg | gtg | ttc | 1584 |
|    | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe |      |
|    |     |     | 515 |     |     |     | 520 |     |     |     |     |     | 525 |     |     |     |      |
| 40 | aat | atg | aat | gcc | cca | gtt | cct | cct | gtt | aat | gaa | cca | gaa | act | ttg | aaa | 1632 |
|    | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys |      |
|    |     | 530 |     |     |     | 535 |     |     |     |     |     | 540 |     |     |     |     |      |
|    | caa | caa | aat | cag | tac | cag | gcc | agt | tat | aac | cag | agc | ttt | tct | agt | cag | 1680 |
| 45 | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln |      |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |      |
|    | cct | cac | caa | gta | gaa | caa | aca | gac | ctt | cag | caa | gaa | cag | ctt | caa | aca | 1728 |
| 50 | Pro | His | Gln | Val | Glu | Gln | Thr | Asp | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr |      |
|    |     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |      |
|    | gtg | gtt | ggc | act | tac | cat | ggg | tcc | cag | gac | cag | ccc | cac | caa | gtg | act | 1776 |
|    | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp | Gln | Pro | His | Gln | Val | Thr |      |
|    |     |     |     | 580 |     |     |     | 585 |     |     |     |     |     | 590 |     |     |      |
| 55 | ggg | aac | cat | cag | cag | cct | ccc | cag | cag | aac | act | gga | ttt | cca | cgt | agc | 1824 |
|    | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser |      |
|    |     |     | 595 |     |     |     | 600 |     |     |     |     |     | 605 |     |     |     |      |

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|    |                                                                                                                                                       |      |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
|    | agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt<br>Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg<br>610 615 620     | 1872 |
| 5  | ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc<br>Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe<br>625 630 635 640 | 1920 |
| 10 | aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac<br>Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn<br>645 650 655     | 1968 |
| 15 | agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc<br>Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly<br>660 665 670     | 2016 |
| 20 | tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag<br>Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln<br>675 680 685     | 2064 |
| 25 | agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc<br>Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro<br>690 695 700     | 2112 |
| 30 | aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa<br>Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn<br>705 710 715                         | 2154 |
|    | tctgattcac aggattatgt ttaaacgccca aaaacacact ggccagtgtta ccataatatg                                                                                   | 2214 |
|    | ttaccagaag agttattatc tatttggact gttttcatcc cataaagaca ggactacaat                                                                                     | 2274 |
|    | tgtcagc                                                                                                                                               | 2281 |
| 35 | <210> 14<br><211> 717<br><212> PRT<br><213> Canis familiaris                                                                                          |      |
| 40 | <400> 14                                                                                                                                              |      |
| 45 |                                                                                                                                                       |      |
| 50 |                                                                                                                                                       |      |
| 55 |                                                                                                                                                       |      |

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

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 5  | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser |  |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| 10 | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu |  |
|    |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 15 | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu |  |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| 20 | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu |  |
|    |     |     |     |     | 165 |     |     |     | 170 |     |     |     |     |     | 175 |     |  |
| 25 | Lys | Gln | Gly | Leu | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| 30 | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| 35 | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp |  |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 40 | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Ser | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 45 | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser |  |
|    |     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
| 50 | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser |  |
|    |     |     | 260 |     |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 55 | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 60 | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn |  |
|    | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| 65 | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| 70 | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| 75 | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
| 5  | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser |  |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
|    | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala |  |
| 10 | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
|    | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys |  |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| 15 | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val | Pro |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
|    | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu |  |
| 20 |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
|    | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu |  |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| 25 | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
|    | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser |  |
| 30 |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
|    | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser |  |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |
| 35 | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe |  |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
|    | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu | Lys |  |
| 40 |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |
|    | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln |  |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |
| 45 | Pro | His | Gln | Val | Glu | Gln | Thr | Asp | Leu | Gln | Gln | Glu | Gln | Leu | Gln | Thr |  |
|    |     |     |     |     | 565 |     |     |     | 570 |     |     |     |     |     | 575 |     |  |
|    | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp | Gln | Pro | His | Gln | Val | Thr |  |
| 50 |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |
|    | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser |  |
|    |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
| 55 | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg |  |

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|    | 610                | 615                     | 620                             |
|----|--------------------|-------------------------|---------------------------------|
| 5  | Gly 625            | Ala Arg Gly Leu Met 630 | Asn Gly Tyr Arg Gly 635         |
|    |                    |                         | Pro Ala Asn Gly Phe 640         |
| 10 | Arg Gly Gly Tyr    | Asp 645                 | Gly Tyr Arg Pro Ser Phe 650     |
|    |                    |                         | Ser Asn Thr Pro Asn 655         |
| 15 | Ser Gly Tyr Thr    | Gln 660                 | Ser Gln Phe Ser 665             |
|    |                    |                         | Ala Pro Arg Asp Tyr Ser Gly 670 |
| 20 | Tyr Gln Arg Asp    | Gly Tyr Gln Gln 680     | Asn Phe Lys Arg Gly 685         |
|    |                    |                         | Ser Gly Gln                     |
| 25 | Ser Gly Pro Arg    | Gly Ala Pro Arg 695     | Gly Arg Gly Gly 700             |
|    |                    |                         | Pro Pro Arg Pro                 |
| 30 | Asn Arg Gly Met    | Pro Gln Met 710         | Asn Thr Gln Gln 715             |
|    |                    |                         | Val Asn                         |
| 35 | <210> 15           |                         |                                 |
|    | <211> 3386         |                         |                                 |
|    | <212> DNA          |                         |                                 |
|    | <213> Bos taurus   |                         |                                 |
| 40 | <220>              |                         |                                 |
|    | <221> CDS          |                         |                                 |
|    | <222> (82)..(2208) |                         |                                 |
|    | <223>              |                         |                                 |
| 45 | <400> 15           |                         |                                 |

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|    |                                                                                                                                                   |     |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|    | cgcggtctcgc cccgtccacc gattgactcg ccgctcttgt ccttcctccc gctctttctt                                                                                | 60  |
| 5  | ctctccccctt acggtttcaa g atg cct tcg gcc acc agc cac agc gga agc<br>Met Pro Ser Ala Thr Ser His Ser Gly Ser<br>1 5 10                             | 111 |
| 10 | ggc agc aag tcg tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg aat<br>Gly Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Asn<br>15 20 25    | 159 |
| 15 | gag gcg ggg gcc ggg gcc gcc gcg ccg gct tcc caa cac ccc atg acc<br>Glu Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Met Thr<br>30 35 40    | 207 |
| 20 | ggc acc ggg gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg<br>Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val<br>45 50 55    | 255 |
| 25 | atc gac aag aaa ctt cgg aac ctg gag aag aaa aag ggc aag ctt gat<br>Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp<br>60 65 70    | 303 |
| 30 | gat tat cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag<br>Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln<br>75 80 85 90 | 351 |
| 35 | ctg gat gcc gtg tct aag tac cag gaa gtc aca aat aac ttg gag ttt                                                                                   | 399 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Leu | Asp | Ala | Val | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe |      |
|    |     |     |     |     | 95  |     |     |     |     | 100 |     |     |     |     | 105 |     |      |
| 5  | gca | aaa | gaa | tta | cag | agg | agt | ttc | atg | gca | tta | agc | caa | gat | att | cag | 447  |
|    | Ala | Lys | Glu | Leu | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln |      |
|    |     |     |     | 110 |     |     |     |     | 115 |     |     |     |     | 120 |     |     |      |
| 10 | aaa | aca | ata | aag | aag | aca | gca | cgt | cgg | gag | cag | ctt | atg | aga | gag | gaa | 495  |
|    | Lys | Thr | Ile | Lys | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu |      |
|    |     |     | 125 |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |      |
| 15 | gct | gaa | cag | aaa | cgt | tta | aaa | aca | gta | ctt | gag | ctg | cag | tat | gtt | ttg | 543  |
|    | Ala | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu |      |
|    |     | 140 |     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     |      |
| 20 | gac | aaa | cta | gga | gat | gat | gaa | gtg | aga | act | gac | ctg | aag | caa | ggg | ttg | 591  |
|    | Asp | Lys | Leu | Gly | Asp | Asp | Glu | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu |      |
|    | 155 |     |     |     |     | 160 |     |     |     |     | 165 |     |     |     |     | 170 |      |
| 25 | aat | gga | gtg | cca | ata | ttg | tct | gaa | gag | gag | ttg | tcg | ttg | tta | gat | gag | 639  |
|    | Asn | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu |      |
|    |     |     |     |     | 175 |     |     |     |     | 180 |     |     |     |     | 185 |     |      |
| 30 | ttc | tac | aaa | tta | gca | gac | cct | gaa | cga | gac | atg | agc | ttg | agg | ttg | aat | 687  |
|    | Phe | Tyr | Lys | Leu | Ala | Asp | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn |      |
|    |     |     |     | 190 |     |     |     |     | 195 |     |     |     |     | 200 |     |     |      |
| 35 | gag | cag | tat | gaa | cat | gcc | tcc | att | cac | ctg | tgg | gac | ttg | ctg | gaa | gga | 735  |
|    | Glu | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly |      |
|    |     |     | 205 |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |      |
| 40 | aag | gaa | aaa | cct | gta | tgt | gga | aca | act | tat | aaa | gct | cta | aag | gaa | att | 783  |
|    | Lys | Glu | Lys | Pro | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile |      |
|    |     | 220 |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     |      |
| 45 | gtt | gag | cgt | gtt | ttc | cag | tca | aac | tac | ttt | gac | agc | acc | cac | aac | cac | 831  |
|    | Val | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His |      |
|    |     | 235 |     |     |     | 240 |     |     |     |     | 245 |     |     |     |     | 250 |      |
| 50 | cag | aat | ggg | ctg | tgt | gag | gaa | gag | gag | gca | gcc | tca | gca | cct | aca | gtt | 879  |
|    | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val |      |
|    |     |     |     |     | 255 |     |     |     |     | 260 |     |     |     |     | 265 |     |      |
| 55 | gaa | gac | cag | gca | gct | gaa | gct | gaa | cct | gag | cca | gtg | gaa | gaa | tat | act | 927  |
|    | Glu | Asp | Gln | Ala | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Val | Glu | Glu | Tyr | Thr |      |
|    |     |     |     | 270 |     |     |     |     | 275 |     |     |     |     | 280 |     |     |      |
| 60 | gaa | caa | aat | gag | gtt | gaa | tca | aca | gag | tat | gta | aat | aga | caa | ttt | atg | 975  |
|    | Glu | Gln | Asn | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met |      |
|    |     |     | 285 |     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |      |
| 65 | gca | gaa | aca | cag | ttc | agc | agt | ggg | gaa | aag | gag | cag | gta | gat | gat | tg  | 1023 |
|    | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Asp | Trp |      |
|    |     | 300 |     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     |      |
| 70 | aca | gtt | gaa | aca | gtt | gag | gtg | gta | aat | tca | ctc | cag | cag | caa | cct | cag | 1071 |
|    | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln |      |
|    |     | 315 |     |     |     | 320 |     |     |     |     |     | 325 |     |     |     | 330 |      |
| 75 | gct | gca | tct | cct | tca | gta | cca | gaa | ccc | cac | tct | ttg | acc | cca | gtg | gct | 1119 |
|    | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala |      |
|    |     |     |     |     | 335 |     |     |     |     | 340 |     |     |     |     | 345 |     |      |
| 80 | caa | gcc | gat | ccc | ctc | gtg | aga | aga | cag | cga | gta | cag | gac | ctt | atg | gca | 1167 |
|    | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala |      |

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|    | 350                                                                                                                                                   | 355  | 360 |  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----|--|
| 5  | caa atg cag ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt<br>Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe<br>365 370 375     | 1215 |     |  |
| 10 | gaa aac cag aca ctt gat cct gcc att gta tct gca cag ccg atg aat<br>Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn<br>380 385 390     | 1263 |     |  |
| 15 | cca gca cag aac atg gac ata ccc cag ctg gtt tgc cct cca gtt cat<br>Pro Ala Gln Asn Met Asp Ile Pro Gln Leu Val Cys Pro Pro Val His<br>395 400 405 410 | 1311 |     |  |
| 20 | tct gaa tct aga ctt gct caa cct aat caa gtt tct gta cag cca gaa<br>Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Ser Val Gln Pro Glu<br>415 420 425     | 1359 |     |  |
| 25 | gct aca cag gtt cct ttg gtt tca tcc aca agt gag gga tat aca gca<br>Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala<br>430 435 440     | 1407 |     |  |
| 30 | tct caa ccc ttg tac caa cct tct cat gct act gac caa cga cca caa<br>Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Asp Gln Arg Pro Gln<br>445 450 455     | 1455 |     |  |
| 35 | aag gaa ccg att gat cag att cag gcg acg atc tct tta aat aca gac<br>Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp<br>460 465 470     | 1503 |     |  |
| 40 | cag act aca gca tca tca tcc ctt cct gct gct tct cag cct caa gtg<br>Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val<br>475 480 485 490 | 1551 |     |  |
| 45 | ttc cag gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta<br>Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val<br>495 500 505     | 1599 |     |  |
| 50 | aat gca gct cca ttc caa tcc atg caa acg gta ttc aat atg aat gcc<br>Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala<br>510 515 520     | 1647 |     |  |
| 55 | cca gtt cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag<br>Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln<br>525 530 535     | 1695 |     |  |
| 60 | tac cag gcc agt tac aac cag agc ttt tcc agt cag cct cac caa gta<br>Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val<br>540 545 550     | 1743 |     |  |
| 65 | gaa caa aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act<br>Glu Gln Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr<br>555 560 565 570 | 1791 |     |  |
| 70 | tat cat ggt tct cag gac cag ccc cat caa gtg act ggt aac cac cag<br>Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr Gly Asn His Gln<br>575 580 585     | 1839 |     |  |
| 75 | cag cct cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat<br>Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr<br>590 595 600     | 1887 |     |  |
| 80 | tac aac agt cgt ggt gtg tct cgt gga ggt tcc cgt ggt gct aga ggc<br>Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly<br>605 610 615     | 1935 |     |  |

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|    |                                                                     |      |
|----|---------------------------------------------------------------------|------|
|    | ttg atg aat gga tac aga gga cct gct aat gga ttc aga gga gga tat     | 1983 |
|    | Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr     |      |
|    | 620 625 630                                                         |      |
| 5  | gat ggt tac cgc cct tca ttc tct act aac act cca aac agt ggt tat     | 2031 |
|    | Asp Gly Tyr Arg Pro Ser Phe Ser Thr Asn Thr Pro Asn Ser Gly Tyr     |      |
|    | 635 640 645 650                                                     |      |
|    | aca caa tct caa ttc agt gct ccc cgg gac tac tct ggc tat cag cgg     | 2079 |
| 10 | Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg     |      |
|    | 655 660 665                                                         |      |
|    | gat gga tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca     | 2127 |
|    | Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro     |      |
|    | 670 675 680                                                         |      |
| 15 | cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg     | 2175 |
|    | Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly     |      |
|    | 685 690 695                                                         |      |
|    | atg ccg caa atg aac act cag caa gtg aat taa tctgattcac aggattatgt   | 2228 |
| 20 | Met Pro Gln Met Asn Thr Gln Gln Val Asn                             |      |
|    | 700 705                                                             |      |
|    | ttaatcgcca aaaacacact ggccagtgtta ccataatatg ttaccagaag agttattatc  | 2288 |
| 25 | tatttggttct cccttttcagg aaacttattg taaagggact gttttcatcc cataaagaca | 2348 |
|    | ggactacaat tgtcagcttt atattacctg gatattggaag gaaactatctt ttactctgca | 2408 |
|    | tgttctgtcc taagcgtcat ottgagcctt gcacatgata ctcagattcc tcacccttgc   | 2468 |
| 30 | ttaggagtaa aacataatat actttaatgg ggtgatattct ccatagttat ttgaagtggc  | 2528 |
|    | ttggataaag caagactgac ttctgacatt ggataaaatc taaaaatcag ccctagagtc   | 2588 |
|    | attcagtggt aactgacaaa actaaaatat ttcccttgaa aggaagatgg aaggagtgga   | 2648 |
| 35 | gtgtggtttg gcagaacaac tgcatttcac agcttttcca cttaaattgg agcactgaac   | 2708 |
|    | atttagatgc ataccgaatt atgcatgggc cctaatacaca cagacaaggc tgggtgccagc | 2768 |
|    | cttaggcttg acacggcagt gttcaccttc tggccagacg actgtggttc aagacacatg   | 2828 |
| 40 | taaattgctt ttttaacagct gatactgtat aagacaaagc caaaatgcaa aattaggctt  | 2888 |
|    | tgattggcac ttttcgaaaa atatgcaaca attaagggat ataactctgga tggccgcttc  | 2948 |
| 45 | tgtacttaat gtgaaatatt tagatacctt tcaaacactt aacagtttct ttgacaatga   | 3008 |
|    | gttttgtaag gattggtagt aaatatcatt ccttatgacg tacattgtct gtcactaatc   | 3068 |
|    | cttgatctt gctgtattgt cacctaaatt ggtacaggta ctgatgaaaa tctaattggat   | 3128 |
| 50 | aatcataaca ctcttggtta catgtttttc ctgcagcctg aaagttttta taagaaaaag   | 3188 |
|    | acatcaaatg cctgctgctg ccaccctttt aaattgctat cttttgaaaa gcaccagtat   | 3248 |
|    | gtgttttaga ttgatttccc tatttttaggg aaatgacagt cagtagtttc acttctgatg  | 3308 |
| 55 | gtataagcaa acaaataaaa catgtttata aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   | 3368 |
|    | aaaaaaaaaa aaaaaaaaaa                                               | 3386 |

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<210> 16  
<211> 708  
<212> PRT  
<213> Bos taurus

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<400> 16

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55

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

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | 225 |     |     |     |     | 230 |     |     |     |     |     | 235 |     |     |     | 240 |
| 5  | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
|    | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Ala | Ala | Glu |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| 10 | Ala | Glu | Pro | Glu | Pro | Val | Glu | Glu | Tyr | Thr | Glu | Gln | Asn | Glu | Val | Glu |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| 15 | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser |
|    |     |     | 290 |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
|    | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Asp | Trp | Thr | Val | Glu | Thr | Val | Glu |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| 20 | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| 25 | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
|    | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| 30 | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp |
|    |     |     | 370 |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| 35 | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Ala | Gln | Asn | Met | Asp |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
|    | Ile | Pro | Gln | Leu | Val | Cys | Pro | Pro | Val | His | Ser | Glu | Ser | Arg | Leu | Ala |
|    |     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| 40 | Gln | Pro | Asn | Gln | Val | Ser | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu |
|    |     |     |     | 420 |     |     |     | 425 |     |     |     |     |     | 430 |     |     |
| 45 | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
|    | Pro | Ser | His | Ala | Thr | Asp | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Ile | Asp | Gln |
|    |     |     | 450 |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| 50 | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| 55 | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser |
|    |     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| 5  | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| 10 | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn |
|    |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| 15 | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Gln |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| 20 | Gln | Glu | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp |
|    |     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| 25 | Gln | Pro | His | Gln | Val | Thr | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn |
|    |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| 30 | Thr | Gly | Phe | Pro | Arg | Ser | Asn | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val |
|    |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| 35 | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg |
|    | 610 |     |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| 40 | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser |
|    | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| 45 | Phe | Ser | Thr | Asn | Thr | Pro | Asn | Ser | Gly | Tyr | Thr | Gln | Ser | Gln | Phe | Ser |
|    |     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     | 655 |     |
| 50 | Ala | Pro | Arg | Asp | Tyr | Ser | Gly | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln | Asn |
|    |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |
| 55 | Phe | Lys | Arg | Gly | Ser | Gly | Gln | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg | Gly |
|    |     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| 60 | Arg | Gly | Gly | Pro | Pro | Arg | Pro | Asn | Arg | Gly | Met | Pro | Gln | Met | Asn | Thr |
|    | 690 |     |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |
| 65 | Gln | Gln | Val | Asn |     |     |     |     |     |     |     |     |     |     |     |     |
|    | 705 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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<223>

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|    |                                                                 |     |
|----|-----------------------------------------------------------------|-----|
|    | atg gag ggc aag ctc gat gat tac caa gag cga atg aac aaa gga gaa | 48  |
|    | Met Glu Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu |     |
|    | 1 5 10 15                                                       |     |
| 5  | agg ctt aat cag gat cag ctg gat gct gtg tct aag tac cag gaa gtc | 96  |
|    | Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val |     |
|    | 20 25 30                                                        |     |
| 10 | aca aat aac ttg gag ttt gcg aaa gaa ttg cag agg agt ttc atg gcg | 144 |
|    | Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala |     |
|    | 35 40 45                                                        |     |
| 15 | ttg agt cag gat att cag aaa aca ata aag aag acg gca cgt cgg gag | 192 |
|    | Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu |     |
|    | 50 55 60                                                        |     |
| 20 | cag ctt atg aga gaa gaa gct gaa cag aaa cgt tta aaa act gta ctt | 240 |
|    | Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu |     |
|    | 65 70 75 80                                                     |     |
| 25 | gag ctg cag tat gtt ttg gac aaa ttg gga gat gaa gaa gtg cga act | 288 |
|    | Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Glu Glu Val Arg Thr |     |
|    | 85 90 95                                                        |     |
| 30 | gac ctg aaa caa ggt ttg aat gga gtg cca ata ctc tct gaa gaa gag | 336 |
|    | Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu |     |
|    | 100 105 110                                                     |     |
| 35 | ttg tcg ctg ttg gat gag ttc tac aag tta gca gac cct gta cgg gac | 384 |
|    | Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Val Arg Asp |     |
|    | 115 120 125                                                     |     |
| 40 | atg agc ttg agg ttg aat gag cag tat gag cat gcc tcc att cac ctg | 432 |
|    | Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu |     |
|    | 130 135 140                                                     |     |
| 45 | tgg gac ttg ctg gaa ggg aag gaa aaa tct gtc tgt gga aca acc tat | 480 |
|    | Trp Asp Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr |     |
|    | 145 150 155 160                                                 |     |
| 50 | aaa gct ctg agg gaa att gtt gag cgt gtt ttc cag tcc aac tac ttt | 528 |
|    | Lys Ala Leu Arg Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe |     |
|    | 165 170 175                                                     |     |
| 55 | gac agc acc cac aac cac cag aat ggg ctc tgt gag gag gaa gag gct | 576 |
|    | Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala |     |
|    | 180 185 190                                                     |     |
| 60 | acc tca gct cca aca gct gaa gac cag gga gct gaa gct gaa cct gag | 624 |
|    | Thr Ser Ala Pro Thr Ala Glu Asp Gln Gly Ala Glu Ala Glu Pro Glu |     |
|    | 195 200 205                                                     |     |
| 65 | cca gca gaa gaa tac act gaa caa agt gaa gtt gaa tca aca gag tat | 672 |
|    | Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr |     |
|    | 210 215 220                                                     |     |
| 70 | gta aat aga cag ttt atg gca gaa gcg cag ttc agt ggt gag aag gag | 720 |
|    | Val Asn Arg Gln Phe Met Ala Glu Ala Gln Phe Ser Gly Glu Lys Glu |     |
|    | 225 230 235 240                                                 |     |
| 75 | cag gtg gat gag tgg aca gtc gag acg gtc gag gtg gta aat tca ctc | 768 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu |      |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |      |
| 5  | cag | cag | caa | cct | cag | gct | gca | tct | cct | tca | gta | ccg | gag | ccc | cac | tct | 816  |
|    | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser |      |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |      |
| 10 | ttg | act | cca | gtg | gct | cag | gca | gat | ccc | ctt | gtg | aga | aga | cag | cga | gta | 864  |
|    | Leu | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val |      |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |      |
| 15 | cag | gac | ctt | atg | gcg | caa | atg | cag | ggg | ccc | tat | aat | ttc | ata | cag | gat | 912  |
|    | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp |      |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |      |
| 20 | tca | atg | ctg | gat | ttt | gaa | aac | cag | aca | ctt | gat | cct | gcc | att | gta | tct | 960  |
|    | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser |      |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |      |
| 25 | gca | cag | cct | atg | aat | cca | gca | cag | aat | atg | gac | atg | ccc | cag | ctg | gtt | 1008 |
|    | Ala | Gln | Pro | Met | Asn | Pro | Ala | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val |      |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |      |
| 30 | tgc | cct | cca | gtt | cat | gct | gaa | tct | aga | ctt | gct | caa | cct | aat | caa | gtt | 1056 |
|    | Cys | Pro | Pro | Val | His | Ala | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val |      |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |      |
| 35 | cct | gta | caa | cca | gaa | gct | aca | cag | gtt | cct | ttg | gtt | tca | tcc | aca | agt | 1104 |
|    | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser |      |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |      |
| 40 | gag | ggg | tat | aca | gca | tct | cag | ccc | ttg | tac | cag | cct | tct | cat | gct | aca | 1152 |
|    | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr |      |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |      |
| 45 | gag | caa | cga | ccg | caa | aag | gaa | ccg | act | gac | cag | atc | cag | gca | aca | atc | 1200 |
|    | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Thr | Asp | Gln | Ile | Gln | Ala | Thr | Ile |      |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |      |
| 50 | tct | tta | aat | aca | gac | cag | act | aca | gca | tca | tca | tcc | ctt | cct | gct | gct | 1248 |
|    | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala |      |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |      |
| 55 | tct | cag | cct | cag | gtg | ttc | cag | gct | ggg | aca | agc | aaa | cct | tta | cac | agc | 1296 |
|    | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser |      |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |      |
| 60 | agt | ggg | atc | aat | gta | aat | gca | gcg | cca | ttc | cag | tcc | atg | caa | acg | gtg | 1344 |
|    | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val |      |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |      |
| 65 | ttc | aac | atg | aat | gcc | ccg | gtt | cct | cct | gtt | aat | gaa | cca | gaa | act | tta | 1392 |
|    | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu |      |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |      |
| 70 | aaa | cag | caa | aat | cag | tac | cag | gcc | agc | tat | aac | cag | agc | ttt | tcc | agt | 1440 |
|    | Lys | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser |      |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |      |
| 75 | ccg | cct | cac | caa | gta | gag | cag | aca | gag | ctt | ccg | caa | gag | cag | ctt | cag | 1488 |
|    | Pro | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Pro | Gln | Glu | Gln | Leu | Gln |      |
|    |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |      |
| 80 | acg | gtg | gtt | ggt | act | tac | cat | gct | tcc | caa | gac | cag | ccc | cat | caa | gtg | 1536 |
|    | Thr | Val | Val | Gly | Thr | Tyr | His | Ala | Ser | Gln | Asp | Gln | Pro | His | Gln | Val |      |

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|    | 500                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 505                                                                                                                          | 510 |  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-----|--|
| 5  | acc ggt aac cac cag cag cct ccc cag cag aac act ggg ttt cca cgt<br>Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg<br>515 520 525                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1584                                                                                                                         |     |  |
|    | agc agt cag ccc tat tac aac agt cgt ggt gtg tct cgt gga ggc tcc<br>Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser<br>530 535 540                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1632                                                                                                                         |     |  |
| 10 | cgt ggt gct aga ggc ttg atg aat gga tac agg ggc cct gcc aat gga<br>Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly<br>545 550 555 560                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1680                                                                                                                         |     |  |
| 15 | ttc aga gga gga tat gat ggt tac cgc cct tog ttc tct aac act cca<br>Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro<br>565 570 575                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1728                                                                                                                         |     |  |
|    | aac agc ggt tac aca cag tct cag ttc agt gct ccc cgg gac tac tct<br>Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser<br>580 585 590                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1776                                                                                                                         |     |  |
| 20 | ggc tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg<br>Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly<br>595 600 605                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1824                                                                                                                         |     |  |
| 25 | cag agt gga ccc cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga<br>Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg<br>610 615 620                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1872                                                                                                                         |     |  |
| 30 | ccc aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa<br>Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn<br>625 630 635                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1917                                                                                                                         |     |  |
| 35 | tctgattcac aggattatct ttaatcgcca aaacacactg gccagtgtac cataatatgt<br>taccagaaga gttattatct atttgttctc cctttcagga aacttattgt aaagggactg<br>ttttcatccc ataaagacag gactacagtt gtcagcttta tattacctgg atagtgaagg<br>aaactatttt tactctgcat gttctgtcct aagcgtcatc ttgagccttg cacatgatac<br>tcagattcct ttcccttgct taggagtaaa acataatata ctttatgggg tgataaatc<br>tccatagtta tttgaagtgg cttggaaaaa gcaagattga cttttgacat tggataaaat<br>ctacaaatca gccctagagt ttcattggtca ttcacaaaac taaaatattt cccttgaaag<br>gaagatggaa ggactggagt gtggtttggc agaacaactg catttcacag cttttcctat<br>taaattggag cactgaatgt taaatgcata ccaaattatg catgggccct taatcacaca<br>tacatggcta ccagctttga cacagcacta ttcattcctct ggccaaacga ctgtgggttaa<br>aaacacgtgt aaattgcttt ttaacagctg atactgtaaa agacaaagct aaaatgcaaa<br>attaggcttt cattggcact tttcgaaaaa tatgcaacaa atttgggatg taatctggat<br>ggccacttct gtacttaatg tgaagtattt agataccttt ttgaacactt aacagtttct<br>tcgacaatga cttttgtaag gattggtagt atatatcatt ccttatgaca tacattgtct<br>gttgctaata cttggatctt gctgtattgt cacctaaatt ggtacaggta ctgatgaaaa<br>tctctcatgg ataaacctaa cactcttcgt cacatgtttt tcctgcagcc tgaaggtttt | 1977<br>2037<br>2097<br>2157<br>2217<br>2277<br>2337<br>2397<br>2457<br>2517<br>2577<br>2637<br>2697<br>2757<br>2817<br>2877 |     |  |

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|   |                                                                   |      |
|---|-------------------------------------------------------------------|------|
|   | taaaaggaaa agatatcaaa tgcctgctgc taccaccctt ttaaattgct atcttttgaa | 2937 |
|   | aagcaccagt atgtgttttt agattgattt ccctatttta gggaaatgac agtcagtagt | 2997 |
| 5 | ttcagttctg atggtataag caaagcaaat aaaacgtgtt tataaaagt gtatcttgaa  | 3057 |
|   | acactgggtg tcaacagcta gcagcttctg tggttcacc cctgccttgt tagtgttacc  | 3117 |
|   | catttatggt tatctccagc agcaatttct cta                              | 3150 |

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<210> 18

<211> 638

<212> PRT

<213> Equus caballus

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<400> 18

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

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Thr | Ser | Ala | Pro | Thr | Ala | Glu | Asp | Gln | Gly | Ala | Glu | Ala | Glu | Pro | Glu |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| 5  | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |
| 10 | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Ala | Gln | Phe | Ser | Gly | Glu | Lys | Glu |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
|    | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| 15 | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| 20 | Leu | Thr | Pro | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| 25 | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
|    | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| 30 | Ala | Gln | Pro | Met | Asn | Pro | Ala | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| 35 | Cys | Pro | Pro | Val | His | Ala | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
|    | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| 40 | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr |
|    |     | 370 |     |     |     |     | 375 |     |     |     | 380 |     |     |     |     |     |
| 45 | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Thr | Asp | Gln | Ile | Gln | Ala | Thr | Ile |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
|    | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala |
|    |     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |
| 50 | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| 55 | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |

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|    |                     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|---------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Phe                 | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Thr | Leu |
|    | 450                 |     |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| 5  | Lys                 | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Ser |
|    | 465                 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
|    | Pro                 | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Pro | Gln | Glu | Gln | Leu | Gln |
| 10 |                     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
|    | Thr                 | Val | Val | Gly | Thr | Tyr | His | Ala | Ser | Gln | Asp | Gln | Pro | His | Gln | Val |
| 15 |                     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
|    | Thr                 | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg |
|    |                     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| 20 | Ser                 | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser |
|    |                     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
|    | Arg                 | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly |
| 25 | 545                 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
|    | Phe                 | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser | Phe | Ser | Asn | Thr | Pro |
| 30 |                     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |
|    | Asn                 | Ser | Gly | Tyr | Thr | Gln | Ser | Gln | Phe | Ser | Ala | Pro | Arg | Asp | Tyr | Ser |
|    |                     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| 35 | Gly                 | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln | Asn | Phe | Lys | Arg | Gly | Ser | Gly |
|    |                     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
|    | Gln                 | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg | Gly | Arg | Gly | Gly | Pro | Pro | Arg |
| 40 |                     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
|    | Pro                 | Asn | Arg | Gly | Met | Pro | Gln | Met | Asn | Thr | Gln | Gln | Val | Asn |     |     |
|    | 625                 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     |     |
| 45 | <210> 19            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 6181          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> DNA           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 50 | <220>               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <221> CDS           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <222> (179)..(2302) |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <223>               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 55 | <400> 19            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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|   |                                                                  |     |
|---|------------------------------------------------------------------|-----|
|   | gctggctggc taagtccctc ccgcgccggc tcttgtcca ctaggagcag ctgagagccg | 60  |
|   | cggggacagg gcgaagcggc ctgcgccac ggagcgcacg tctctgttct caacgcagca | 120 |
| 5 | ccacccttgc cccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg   | 178 |

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|    |                                                                 |     |
|----|-----------------------------------------------------------------|-----|
|    | atg ccc tcg gcc acc agc cac agc gga agc ggc agc aaa tcg tcg gga | 226 |
|    | Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly |     |
|    | 1 5 10 15                                                       |     |
| 5  | ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag gcg gcg gcc ggg gca | 274 |
|    | Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala |     |
|    | 20 25 30                                                        |     |
| 10 | gct gcg ccg gct tct cag cat ccg gca acc ggc acc ggc gcc gtc cag | 322 |
|    | Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln |     |
|    | 35 40 45                                                        |     |
| 15 | acc gag gcc atg aag cag att ctc ggc gta atc gac aag aaa ctt cgg | 370 |
|    | Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg |     |
|    | 50 55 60                                                        |     |
| 20 | aac ctg gag aag aaa aag ggt aaa ctt gat gat tac cag gaa cga atg | 418 |
|    | Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met |     |
|    | 65 70 75 80                                                     |     |
| 25 | aat aaa ggg gaa agg ctc aat caa gac cag ctg gat gcc gta tct aag | 466 |
|    | Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys |     |
|    | 85 90 95                                                        |     |
| 30 | tac cag gaa gtc aca aat aat ttg gag ttt gca aag gaa tta cag agg | 514 |
|    | Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg |     |
|    | 100 105 110                                                     |     |
| 35 | agt ttc atg gca tta agt caa gat att cag aaa aca ata aag aag aca | 562 |
|    | Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr |     |
|    | 115 120 125                                                     |     |
| 40 | gca cgt ccg gaa cag ctt atg aga gaa gaa gca gaa cag aag cgc tta | 610 |
|    | Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu |     |
|    | 130 135 140                                                     |     |
| 45 | aaa act gta ctt gag tta cag tat gta ttg gat aag ctg gga gat gat | 658 |
|    | Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp |     |
|    | 145 150 155 160                                                 |     |
| 50 | gat gtg aga aca gat ctg aaa caa ggt ttg agt gga gtg cca ata ttg | 706 |
|    | Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu |     |
|    | 165 170 175                                                     |     |
| 55 | tct gag gag gag ttg tca ttg ctg gat gag ttc tac aag ctc gta gat | 754 |
|    | Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp |     |
|    | 180 185 190                                                     |     |
| 60 | cct gag cgt gac atg agt tta agg tta aat gag cag tat gaa cat gcc | 802 |
|    | Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala |     |
|    | 195 200 205                                                     |     |
| 65 | tca att cac ttg tgg gat ttg ctg gaa ggg aaa gaa aag cct gtg tgt | 850 |
|    | Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys |     |
|    | 210 215 220                                                     |     |
| 70 | gga aca acc tat aaa gct cta aag gaa att gtt gag cgt gtt ttc cag | 898 |
|    | Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln |     |
|    | 225 230 235 240                                                 |     |
| 75 | tca aac tac ttt gat agc act cac aat cat caa aat ggg ttg tgt gag | 946 |
|    | Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu |     |
|    | 245 250 255                                                     |     |

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[illegible]

## EP 2 740 489 B1

|    |                                                                                                                                    |      |
|----|------------------------------------------------------------------------------------------------------------------------------------|------|
|    | Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn                                                                    |      |
|    | 515 520 525                                                                                                                        |      |
| 5  | gaa cca gaa acg tta aaa caa cag agt cag tac cag gcc act tat aac<br>Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn | 1810 |
|    | 530 535 540                                                                                                                        |      |
| 10 | cag agt ttt tcc agt cag cct cac caa gtg gaa caa aca gag ctt caa<br>Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln | 1858 |
|    | 545 550 555 560                                                                                                                    |      |
| 15 | caa gac caa ctg caa acg gtg gtt ggc act tac cat gga tcc cag gac<br>Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp | 1906 |
|    | 565 570 575                                                                                                                        |      |
| 20 | cag cct cat caa gtg cct ggt aac cac cag caa ccc cca cag cag aac<br>Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn | 1954 |
|    | 580 585 590                                                                                                                        |      |
| 25 | act ggc ttt cca cgt agc agt cag cct tat tac aac agt cgt ggg gta<br>Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val | 2002 |
|    | 595 600 605                                                                                                                        |      |
| 30 | tct cga gga ggg tct cgt ggt gcc aga ggc ttg atg aat gga tac agg<br>Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg | 2050 |
|    | 610 615 620                                                                                                                        |      |
| 35 | ggc cct gcc aat gga ttt aga gga gga tat gat ggt tac cgc cct tca<br>Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser | 2098 |
|    | 625 630 635 640                                                                                                                    |      |
| 40 | ttc tcg aac act cca aac agt ggt tat tca cag tct cag ttc act gct<br>Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala | 2146 |
|    | 645 650 655                                                                                                                        |      |
| 45 | ccc cgg gac tac tct ggt tac cag cgg gat gga tat cag cag aat ttc<br>Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe | 2194 |
|    | 660 665 670                                                                                                                        |      |
| 50 | aag cga ggc tct ggg cag agt gga cca cgg gga gcc cca cga ggt cgt<br>Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg | 2242 |
|    | 675 680 685                                                                                                                        |      |
| 55 | gga ggg ccc cca aga ccc aac aga ggg atg ccg caa atg aac act cag<br>Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln | 2290 |
|    | 690 695 700                                                                                                                        |      |
| 60 | caa gtg aat taa tgtgatacac aggattatgt ttaatcgcca aaaacacact<br>Gln Val Asn                                                         | 2342 |
|    | 705                                                                                                                                |      |
| 65 | ggccagtgtta ccataatatg ttaccagaag agttattatc tatttggttct ccctttcagg                                                                | 2402 |
| 70 | aaacttatttg taaagggact gttttcatcc cataaagaca ggactgcaat tgtcagcttt                                                                 | 2462 |
| 75 | acattacctg gatatggaag gaaactatatt ttattctgca tgttctgtcc taagcgtcat                                                                 | 2522 |
| 80 | cttgagcctt gcacacaata caatactcag attcctcacc cttgcttagg agtaaaacat                                                                  | 2582 |
| 85 | tatatactta tgggggtgata atatctccat agttagttga agtggcttgg aaaaaaatg                                                                  | 2642 |
| 90 | caagattgaa tttttgacct tggataaaat ctacaatcag ccctagaact attcagtggt                                                                  | 2702 |
| 95 | aattgacaaa gttaaagcat tttctttgaa aggaagatgg aaggagtgga gtgtggttta                                                                  | 2762 |

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|    |            |             |             |             |            |             |      |
|----|------------|-------------|-------------|-------------|------------|-------------|------|
|    | gcaaaactgc | atttcatagc  | tttccatta   | aattggagca  | ccgacagatt | aaaagcatac  | 2822 |
|    | caaattatgc | atgggtcctt  | actcacacaa  | gtgaggctgg  | ctaccagcct | tgacatagca  | 2882 |
| 5  | ctcactagtc | ttctggccaa  | acgactgtga  | ttaaaacaca  | tgtaaattgc | tcttttagtag | 2942 |
|    | tggtactgt  | gtaagacaaa  | gccaaattgc  | aaatcaggct  | ttgattggct | cttctggaaa  | 3002 |
|    | atatgcatca | aatatggggg  | ataatctgga  | tgggtctgtg  | ctgtgctcaa | tgtgaactat  | 3062 |
| 10 | ttagatacct | ttggaacact  | taacagtttc  | tctgaacaat  | gacttacatg | gggattggtc  | 3122 |
|    | ctgtttgtca | ttcctcacca  | taattgcatt  | gtcatcacta  | atccttggat | cttgctgtat  | 3182 |
|    | tgttactcaa | attggtaata  | ggtactgatg  | gaaatcgcta  | atggatggat | aatcataaca  | 3242 |
| 15 | cttttggta  | catgttttct  | cctgcagcct  | gaaagtctct  | aaagaaaaag | atatcaaatg  | 3302 |
|    | cctgctgcta | ccaccctttt  | aaattgctat  | ctttagaaaa  | gcaccgggat | gtgttttaga  | 3362 |
|    | ttcatttccc | tgtttttaggg | aaatgacagg  | cagtagtttc  | agttctgatg | gcaaaacaaa  | 3422 |
| 20 | taaaaacatg | tttctaaaag  | ttgtatcttg  | aaacactggg  | gttcaacagc | tagcagctaa  | 3482 |
|    | agtaattcaa | cccatgcatt  | gctagtgtca  | cagcctttgg  | ttatgtctag | tagctgtttc  | 3542 |
|    | tgaagtatct | tcatttatct  | tttgtcaaat  | ttaaccctgt  | ttgaattctc | tcctttcctc  | 3602 |
| 25 | aaggagacac | ttatgttcaa  | agtgttgatt  | ctttgcctta  | ggtgcataga | gagtagacag  | 3662 |
|    | tttggagatg | gaaagggttag | cagtgaacta  | gccatatgtt  | ctgtgttgga | atttgtgcta  | 3722 |
|    | gcagtttgag | cactagctct  | gcgtgcctat  | gaactgaatg  | ctgcttgtcc | cattccattt  | 3782 |
| 30 | tatgtcatgg | agaaataatt  | ccacttggtg  | acacaaaggc  | taagttaatg | ttattttctg  | 3842 |
|    | tacagaaatt | aaattttact  | tttagccttt  | tgtaaaacttt | tttttttttt | ttccaagccg  | 3902 |
|    | gtatcagcta | ctcaaaacaa  | ttctcagata  | ttcatcatta  | gacaactgga | gtttttgctg  | 3962 |
| 35 | gttttgtagc | ctactaaaac  | tgctgaggct  | gttgaacatt  | ccacattcaa | aagttttgta  | 4022 |
|    | gggtggtgga | taatggggaa  | gcttcaatgt  | ttatttttaa  | ataaataaaa | taagttcttg  | 4082 |
|    | acttttctca | tgtgtggtta  | tggtacatca  | tattggaagg  | gttatctgtt | tacttttgcc  | 4142 |
| 40 | aagactatct | tgccagcacc  | tacacttggt  | tgctttaaaa  | gacaactacc | tgggatgtac  | 4202 |
|    | cacaaccata | tggttaattgt | attttattgg  | gatggataaa  | atgtttgtgg | tttattggat  | 4262 |
|    | aatccctaga | tggtgtgtta  | cgtgtgtaga  | atataatctt  | atgatagtaa | gaaagcaaaa  | 4322 |
| 45 | ttgaagaaaa | taagtttagt  | attgaatttg  | agttctgaag  | tgaattcagg | gaatgtctca  | 4382 |
|    | cgtttcgggc | ttctacccaa  | agtgtagggc  | agaagggtga  | aaagttgttt | gtagtttgac  | 4442 |
|    | ttgtttatct | tttaagttgc  | ttattccttt  | caacagcaac  | atatcattag | ctgtcattct  | 4502 |
|    | accattgcag | ttctagttag  | ttttaacgtc  | tgcatcgaag  | actgttttaa | aagcaacctc  | 4562 |
|    | actggacaga | gaactgctaa  | agtcttttcc  | ttaagatctg  | agtctttgtt | actcagtatc  | 4622 |
| 50 | ttctataata | tgcaaagtct  | tgtctagagg  | cagaagacct  | tttgtttggg | caagtgtgta  | 4682 |
| 55 | ttttaccaga | gtacagggaa  | ctgatgggtcc | tacatgtctc  | ttagttagtg | aagactataa  | 4742 |

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|    |              |             |             |             |             |             |      |
|----|--------------|-------------|-------------|-------------|-------------|-------------|------|
|    | aatcttttgt   | acatgcacaa  | ttcacagtat  | gttttagatac | cacgtgtata  | atgccccccc  | 4802 |
|    | ctccccccagg  | tagcatgccca | ttgatgactt  | tttgcttagg  | gccattttat  | taccagggcc  | 4862 |
| 5  | ttaatatattcc | taaaaagatg  | atTTTTTTTtc | atccttttctc | ctctttttgat | cattgtatct  | 4922 |
|    | tgatattaaa   | aacatgacct  | tccaatgatt  | gtagtaaatt  | aacttctata  | gttcttttgt  | 4982 |
| 10 | ctctatatgt   | attcatatat  | atgctattgt  | atagagactt  | caaggagaca  | tggagatgca  | 5042 |
|    | tgcttattct   | caggttcatt  | cactaagggtg | cttggcagac  | aaccagtttc  | taagtgcaga  | 5102 |
|    | atgtagttaa   | gcagcttcat  | atatgtgccca | ggcaatttgt  | tttgttaaat  | tttcatctac  | 5162 |
| 15 | ttaaggaaat   | agggtattgt  | agcttaggct  | gatcataccc  | ttcatttcaa  | ccttaagctc  | 5222 |
|    | tcaacctgca   | tccatccgac  | ttgagctatt  | aagtacttta  | gttttatcga  | gtataagtta  | 5282 |
|    | acagaaaaag   | taaattaagc  | tttgccttta  | ctatttttgaa | tttatataca  | ttctggaaaa  | 5342 |
| 20 | acttagaaac   | tgttgtatat  | ttcattagat  | taaattatat  | gaaaatgtga  | ttgttttatag | 5402 |
|    | caaagcctgt   | gagttgcata  | caccctaagg  | aaaactcctt  | aagtgctcct  | tgaagagaga  | 5462 |
| 25 | agaaacaatt   | ctgggtctgg  | tctttttaag  | aacaaagcta  | gactactgta  | tgtagcact   | 5522 |
|    | gtacattaat   | agtctgttgt  | gaagcttgag  | cagtttcctg  | catagccttg  | atccttcacc  | 5582 |
|    | gttggcattg   | aaaatagcag  | tatccctgat  | gtacttaaaa  | cttaaagtca  | ggttttggta  | 5642 |
| 30 | tattttatttg  | taagtcttaa  | tttcctctaa  | atactatatc  | tcttttagcga | gacaacctga  | 5702 |
|    | aattttattag  | cacatttggg  | tatctcttgc  | ttggcattat  | ggccagtgtt  | aactattcag  | 5762 |
|    | tggtgaaaaa   | attaccctc   | aagacactgg  | agtgaccca   | gatgtgtgta  | gtaagtggca  | 5822 |
| 35 | tggttcaact   | gtgtggttaa  | tgataaatat  | atgacttagt  | cggtatgatc  | tggaaagact  | 5882 |
|    | tgattgaaag   | ataattcagc  | tgacataagg  | atgagtgagg  | agtggcaaac  | tggataaaag  | 5942 |
| 40 | agtcaagaga   | cctgtattcc  | agtgactcct  | gttttgttta  | agcattagca  | agatctgtct  | 6002 |
|    | ggggaaactg   | gatagggcag  | ttttcttcca  | tgtttagttt  | ttgtctcaac  | atttgaagc   | 6062 |
|    | tattgaaggt   | tttaaaatgg  | tgtgtattgt  | ttttttttgg  | gggggggggtg | gccagaatag  | 6122 |
| 45 | tgggtcatct   | aataaaaactg | ccattttaaaa | gatcaaaaaa  | aaaaaaaaaa  | aaaaaaaaaa  | 6181 |

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<212> PRT

50 <213> Mus musculus

<400> 20

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| Met | Pro | Ser | Ala | Thr | Ser | His | Ser | Gly | Ser | Gly | Ser | Lys | Ser | Ser | Gly |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5 | Pro | Pro | Pro | Pro | Ser | Gly | Ser | Ser | Gly | Ser | Glu | Ala | Ala | Ala | Gly | Ala |
|   |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Ala | Ala | Pro | Ala | Ser | Gln | His | Pro | Ala | Thr | Gly | Thr | Gly | Ala | Val | Gln |  |
|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 5  | Thr | Glu | Ala | Met | Lys | Gln | Ile | Leu | Gly | Val | Ile | Asp | Lys | Lys | Leu | Arg |  |
|    |     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
|    | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu | Arg | Met |  |
| 10 |     | 65  |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
|    | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val | Ser | Lys |  |
|    |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 15 | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu | Gln | Arg |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |  |
|    | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr |  |
| 20 |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
|    | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu |  |
|    |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 25 | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp |  |
|    |     | 145 |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
|    | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser | Gly | Val | Pro | Ile | Leu |  |
| 30 |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
|    | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Val | Asp |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     |     | 190 |     |  |
| 35 | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
|    | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys |  |
| 40 |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
|    | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln |  |
|    |     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 45 | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu |  |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
|    | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu |  |
| 50 |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
|    | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 55 | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser |  |

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|    | 290 |     |     |     |     | 295 |     |     |     |     |     | 300 |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| 5  | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
|    | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| 10 | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ser | Asp | Pro | Leu | Val |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
| 15 | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
|    | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp |  |
|    | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
| 20 | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp |  |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
| 25 | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val | His | Ser | Glu | Ser | Arg | Leu | Ala |  |
|    |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     |     | 415 |     |  |
|    | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu |  |
|    |     |     |     | 420 |     |     |     | 425 |     |     |     |     |     | 430 |     |     |  |
| 30 | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln |  |
|    |     | 435 |     |     |     |     | 440 |     |     |     |     |     | 445 |     |     |     |  |
| 35 | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Met | Asp | Gln |  |
|    | 450 |     |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
|    | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
| 40 | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser |  |
|    |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     |     | 495 |     |  |
| 45 | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln |  |
|    |     |     |     | 500 |     |     |     | 505 |     |     |     |     |     | 510 |     |     |  |
|    | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Ala | Asn |  |
|    |     | 515 |     |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
| 50 | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Ser | Gln | Tyr | Gln | Ala | Thr | Tyr | Asn |  |
|    | 530 |     |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |
| 55 | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Gln |  |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Gln | Asp | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp |  |
|    |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |
| 5  | Gln | Pro | His | Gln | Val | Pro | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn |  |
|    |     |     |     | 580 |     |     |     | 585 |     |     |     |     |     | 590 |     |     |  |
| 10 | Thr | Gly | Phe | Pro | Arg | Ser | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val |  |
|    |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
| 15 | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg |  |
|    |     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |
| 20 | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser |  |
|    | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |  |
| 25 | Phe | Ser | Asn | Thr | Pro | Asn | Ser | Gly | Tyr | Ser | Gln | Ser | Gln | Phe | Thr | Ala |  |
|    |     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     |     |     |  |
| 30 | Pro | Arg | Asp | Tyr | Ser | Gly | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln | Asn | Phe |  |
|    |     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |  |
| 35 | Lys | Arg | Gly | Ser | Gly | Gln | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg | Gly | Arg |  |
|    |     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |  |
| 40 | Gly | Gly | Pro | Pro | Arg | Pro | Asn | Arg | Gly | Met | Pro | Gln | Met | Asn | Thr | Gln |  |
|    |     | 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |  |
| 45 | Gln | Val | Asn |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
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|    | tctccccgta cgtctcctga cttgctggta ttgtccttcc ctcccgcgttt tttcctctcc | 120 |
| 5  | tctcttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc    | 171 |
|    | Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly                        |     |
|    | 1 5 10                                                             |     |
| 10 | agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag    | 219 |
|    | Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu    |     |
|    | 15 20 25                                                           |     |
| 15 |                                                                    |     |
| 20 |                                                                    |     |
| 25 |                                                                    |     |
| 30 |                                                                    |     |
| 35 |                                                                    |     |
| 40 |                                                                    |     |
| 45 |                                                                    |     |
| 50 |                                                                    |     |
| 55 |                                                                    |     |

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|    |                                                                 |      |
|----|-----------------------------------------------------------------|------|
|    | gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc | 267  |
|    | Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly |      |
|    | 30 35 40                                                        |      |
| 5  | acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc | 315  |
|    | Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile |      |
|    | 45 50 55                                                        |      |
| 10 | gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat | 363  |
|    | Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp |      |
|    | 60 65 70 75                                                     |      |
|    | tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg | 411  |
|    | Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu |      |
|    | 80 85 90                                                        |      |
| 15 | gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca | 459  |
|    | Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala |      |
|    | 95 100 105                                                      |      |
| 20 | aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa | 507  |
|    | Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys |      |
|    | 110 115 120                                                     |      |
|    | aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca | 555  |
|    | Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala |      |
|    | 125 130 135                                                     |      |
| 25 | gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat | 603  |
|    | Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp |      |
|    | 140 145 150 155                                                 |      |
| 30 | aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt | 651  |
|    | Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser |      |
|    | 160 165 170                                                     |      |
|    | gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc | 699  |
|    | Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe |      |
|    | 175 180 185                                                     |      |
| 35 | tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag | 747  |
|    | Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu |      |
|    | 190 195 200                                                     |      |
| 40 | cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa | 795  |
|    | Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys |      |
|    | 205 210 215                                                     |      |
| 45 | gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt | 843  |
|    | Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val |      |
|    | 220 225 230 235                                                 |      |
|    | gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa | 891  |
|    | Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln |      |
|    | 240 245 250                                                     |      |
| 50 | aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag | 939  |
|    | Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu |      |
|    | 255 260 265                                                     |      |
| 55 | gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag | 987  |
|    | Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu |      |
|    | 270 275 280                                                     |      |
|    | caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca | 1035 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala |      |
|    | 285 |     |     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     |      |
| 5  | gaa | aca | cag | ttc | agc | agt | ggg | gag | aag | gag | caa | gtg | gat | gag | tgg | aca | 1083 |
|    | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr |      |
|    | 300 |     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |      |
|    | ggt | gaa | aca | gtt | gag | gtt | gta | aac | tca | ctc | cag | cag | caa | cct | cag | gct | 1131 |
|    | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala |      |
| 10 |     |     |     |     | 320 |     |     |     |     | 325 |     |     |     |     | 330 |     |      |
|    | gcg | tcc | cct | tca | gtc | cca | gag | ccc | cac | tct | ttg | act | cca | gtg | gct | cag | 1179 |
|    | Ala | Ser | Pro | Ser | Val | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln |      |
|    |     |     |     | 335 |     |     |     |     | 340 |     |     |     |     | 345 |     |     |      |
| 15 | tca | gat | cca | ctt | gtg | aga | agg | cag | cgt | gta | caa | gat | ctt | atg | gca | caa | 1227 |
|    | Ser | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln |      |
|    |     |     | 350 |     |     |     |     | 355 |     |     |     |     | 360 |     |     |     |      |
|    | atg | caa | ggg | ccc | tat | aat | ttc | ata | cag | gat | tca | atg | ttg | gat | ttt | gaa | 1275 |
|    | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu |      |
| 20 |     | 365 |     |     |     |     | 370 |     |     |     |     | 375 |     |     |     |     |      |
|    | aat | cag | acg | ctt | gat | cct | gcc | att | gta | tcc | gca | cag | cct | atg | aac | cct | 1323 |
|    | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro |      |
|    | 380 |     |     |     |     | 385 |     |     |     |     | 390 |     |     |     |     | 395 |      |
| 25 | acc | cag | aac | atg | gat | atg | cct | cag | ctg | gtt | tgc | cct | cag | gtt | cat | tct | 1371 |
|    | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val | His | Ser |      |
|    |     |     |     | 400 |     |     |     |     | 405 |     |     |     |     | 410 |     |     |      |
|    | gaa | tct | aga | ctt | gcc | caa | tct | aat | caa | gtt | cct | gta | caa | cca | gaa | gcc | 1419 |
|    | Glu | Ser | Arg | Leu | Ala | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala |      |
| 30 |     |     |     | 415 |     |     |     | 420 |     |     |     |     | 425 |     |     |     |      |
|    | aca | cag | gtt | cct | ttg | gtt | tca | tcc | aca | agt | gag | ggg | tat | aca | gca | tct | 1467 |
|    | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser |      |
|    |     |     | 430 |     |     |     | 435 |     |     |     |     |     | 440 |     |     |     |      |
| 35 | cag | ccc | ttg | tac | cag | cca | tct | cat | gct | acg | gag | cag | cgg | ccg | cag | aaa | 1515 |
|    | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys |      |
|    |     | 445 |     |     |     |     | 450 |     |     |     |     | 455 |     |     |     |     |      |
|    | gag | cca | atg | gat | cag | att | cag | gca | aca | ata | tct | ttg | aat | aca | gac | cag | 1563 |
|    | Glu | Pro | Met | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln |      |
| 40 |     | 460 |     |     |     | 465 |     |     |     | 470 |     |     |     |     |     | 475 |      |
|    | act | aca | gca | tcc | tca | tcc | ctt | cct | gct | gct | tct | cag | cct | caa | gtg | ttc | 1611 |
|    | Thr | Thr | Ala | Ser | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe |     |      |
|    |     |     |     | 480 |     |     |     |     | 485 |     |     |     |     | 490 |     |     |      |
| 45 | cag | gct | ggg | aca | agt | aaa | cct | ttg | cac | agc | agt | gga | atc | aat | gta | aat | 1659 |
|    | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn |      |
|    |     |     |     | 495 |     |     |     |     | 500 |     |     |     |     | 505 |     |     |      |
|    | gca | gct | cca | ttc | cag | tcc | atg | caa | acg | gtg | ttc | aat | atg | aat | gct | cca | 1707 |
|    | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro |      |
| 50 |     |     | 510 |     |     |     |     | 515 |     |     |     |     | 520 |     |     |     |      |
|    | gtc | cct | cct | gct | aat | gaa | cca | gaa | acg | tta | aaa | caa | cag | agt | cag | tac | 1755 |
|    | Val | Pro | Pro | Ala | Asn | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Ser | Gln | Tyr |      |
|    |     | 525 |     |     |     | 530 |     |     |     |     |     | 535 |     |     |     |     |      |
| 55 | cag | gcc | act | tat | aac | cag | agt | ttt | tcc | agt | cag | cct | cac | caa | gtg | gaa | 1803 |
|    | Gln | Ala | Thr | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu |      |

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|    | 540                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 545 | 550 | 555 |                                                                                              |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|----------------------------------------------------------------------------------------------|
| 5  | caa aca gag ctt caa caa gac caa ctg caa acg gtg gtt ggc act tac<br>Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr<br>560 565 570                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 1851                                                                                         |
|    | cat gga tcc cag gac cag cct cat caa gtg cct ggt aac cac cag caa<br>His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln<br>575 580 585                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 1899                                                                                         |
| 10 | ccc cca cag cag aac act ggc ttt cca cgt agc agt cag cct tat tac<br>Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr<br>590 595 600                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 1947                                                                                         |
| 15 | aac agt cgt ggg gta tct cga gga ggg tct cgt ggt gcc aga ggc ttg<br>Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu<br>605 610 615                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 1995                                                                                         |
| 20 | atg aat gga tac agg ggc cct gcc aat gga ttt aga gga gga tat gat<br>Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp<br>620 625 630 635                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |     |     |     | 2043                                                                                         |
| 25 | ggg tac cgc cct tca ttc tcg aac act cca aac agt ggt tat tca cag<br>Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln<br>640 645 650                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 2091                                                                                         |
| 30 | tct cag ttc act gct ccc cgg gac tac tct ggt tac cag cgg gat gga<br>Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly<br>655 660 665                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 2139                                                                                         |
| 35 | tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga<br>Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly<br>670 675 680                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 2187                                                                                         |
| 40 | gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg<br>Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro<br>685 690 695                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |     |     | 2235                                                                                         |
| 45 | caa atg aac act cag caa gtg aat taa tgtgatacac aggattatgt<br>Gln Met Asn Thr Gln Gln Val Asn<br>700 705                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |     |     |     | 2282                                                                                         |
| 50 | ttaatcgcca aaaacacact ggccagtgtgta ccataatatg ttaccagaag agttattatc<br>tattttgttct ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca<br>ggactgcaat tgtcagcttt acattacctg gatatggaag gaaactatgt ttattctgca<br>tgttctgtcc taagcgtcat cttgagcctt gcacacaata caatactcag attcctcacc<br>cttgcttagg agtaaaacat tatatactta tggggtgata atatctccat agttagttga<br>agtggcttgg aaaaaaatg caagattgaa tttttgacct tggataaaat ctacaatcag<br>ccctagaact attcagtggt aattgacaaa gttaaagcat tttctttgaa aggaagatgg<br>aaggagtgga gtgtgggttta gcaaaactgc atttcatagc tttccatta aattggagca<br>ccgacagatt aaaagcatac caaattatgc atgggtcctt actcacacaa gtgaggctgg<br>ctaccagcct tgacatagca ctactagtc ttctggccaa acgactgtga ttaaaacaca<br>tgtaaattgc tcttttagtag tggatactgt gtaagacaaa gccaaattgc aaatcaggct<br>ttgattggct cttctggaaa atatgcatca aatatggggg ataactctgga tgggctgctg |     |     |     | 2342<br>2402<br>2462<br>2522<br>2582<br>2642<br>2702<br>2762<br>2822<br>2882<br>2942<br>3002 |

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|    |             |            |             |            |             |             |      |
|----|-------------|------------|-------------|------------|-------------|-------------|------|
|    | ctgtgctcaa  | tgtgaactat | ttagatacct  | ttggaacact | taacagtttc  | tctgaacaat  | 3062 |
|    | gacttacatg  | gggattggtc | ctgtttgtca  | ttcctcacca | taattgcatt  | gtcatcacta  | 3122 |
| 5  | atccttggat  | cttgctgtat | tgttactcaa  | attggtaata | ggtagctgatg | gaaatcgcta  | 3182 |
|    | atggatggat  | aatcataaca | cttttgggtca | catgttttct | cctgcagcct  | gaaagtctct  | 3242 |
|    | aaagaaaaag  | atatcaaagt | cctgctgcta  | ccaccctttt | aaattgctat  | ctttagaaaa  | 3302 |
| 10 | gcaccgggat  | gtgttttaga | ttcatttccc  | tgttttaggg | aaatgacagg  | cagtagtttc  | 3362 |
|    | agttctgatg  | gcaaaacaaa | taaaaacatg  | tttctaaaag | ttgtatcttg  | aaacactggt  | 3422 |
|    | gttcaacagc  | tagcagctaa | agtaattcaa  | cccatgcatt | gctagtgtca  | cagcctttgg  | 3482 |
| 15 | ttatgtctag  | tagctgtttc | tgaagtatct  | tcatttatct | tttgtcaa    | tttaaccctgt | 3542 |
|    | ttgaattctc  | tcctttcctc | aaggagacac  | ttatgttcaa | agtgttgatt  | ctttgcctta  | 3602 |
|    | ggtagcataga | gagtagacag | tttggagatg  | gaaaggtag  | cagtgactta  | gccatatgtt  | 3662 |
| 20 | ctgtgttgga  | atttgtgcta | gcagtttgag  | cactagctct | gcgtgcctat  | gaactgaatg  | 3722 |
|    | ctgcttgtcc  | cattccattt | tatgtcatgg  | agaaataatt | ccacttggtg  | acacaaaggc  | 3782 |
| 25 | taagttaatg  | ttattttctg | tacagaaatt  | aaattttact | tttagccttt  | tgtaaacttt  | 3842 |
|    | tttttttttt  | ttccaagccg | gtatcagcta  | ctcaaaacaa | ttctcagata  | ttcatcatta  | 3902 |
|    | gacaactgga  | gtttttgctg | gtttttagtc  | ctactaaaac | tgttgaggct  | gttgaacatt  | 3962 |
| 30 | ccacattcaa  | aagttttgta | gggtgggtga  | taatggggaa | gcttcaatgt  | ttattttaaa  | 4022 |
|    | ataaataaaa  | taagtctctg | acttttctca  | tgtgtggtta | tggtagatca  | tattggaagg  | 4082 |
|    | gttatctgtt  | tacttttgcc | aagactatct  | tgccagcacc | tacacttgtg  | tgcttttaaaa | 4142 |
| 35 | gacaactacc  | tgggatgtac | cacaaccata  | tgttaattgt | attttattgg  | gatggataaa  | 4202 |
|    | atgtttgtgg  | tttattggat | aatccctaga  | tgggtgtgta | cgtgtgtaga  | atataatttt  | 4262 |
|    | atgatagtaa  | gaaagcaaaa | ttgaagaaaa  | taagttagt  | attgaatttg  | agttctgaag  | 4322 |
| 40 | tgaattcagg  | gaatgtctca | cgtttcgggc  | ttctacccaa | agtgtagggc  | agaagggtga  | 4382 |
|    | aaagtgtgtt  | gtagtttgac | ttgtttatct  | tttaagttgc | ttattccttt  | caacagcaac  | 4442 |
|    | atatcattag  | ctgtcattct | accattgcag  | ttctagttag | ttttaacgtc  | tgcatcctaa  | 4502 |
| 45 | actgttttaa  | aagcaacctc | actggacaga  | gaactgctaa | agtcttttcc  | ttaagatctg  | 4562 |
|    | agtctttgtt  | actcagtatc | ttctataata  | tgcaaatgct | tgtctagagg  | cagaagacct  | 4622 |
|    | tttgtttggg  | caagtgtgta | ttttaccaga  | gtacagggaa | ctgatgggtc  | tacatgtctc  | 4682 |
| 50 | ttagtgtagt  | aagactataa | aatcttttgt  | acatgcacaa | ttcacagtat  | gtttagatac  | 4742 |
|    | cacgtgtata  | atgccccccc | ctccccagg   | tagcatgcca | ttgatgactt  | tttgcttagg  | 4802 |
| 55 | gccattttat  | taccaggggc | ttaatattcc  | taaaaagatg | attttttttc  | atcctttctc  | 4862 |
|    | ctcttttgat  | cattgtatct | tgatattaaa  | aacatgacct | tccaatgatt  | gtagtaaatt  | 4922 |

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|    |                                                                     |      |
|----|---------------------------------------------------------------------|------|
|    | aacttctata gttcttttgt ctctatatgt attcatatat atgctattgt atagagactt   | 4982 |
|    | caaggagaca tggagatgca tgcttattct caggttcatt cactaagggtg cttggcagac  | 5042 |
| 5  | aaccagtttc taagtgcaga atgtagttaa gcagcttcat atatgtgcca ggcaatttgt   | 5102 |
|    | tttgttaaat tttcatctac ttaaggaaat agggatttgt agcttaggct gatcataccc   | 5162 |
| 10 | ttcatttcaa ccttaagctc tcaacctgca tccatccgac ttgagctatt aagtacttta   | 5222 |
|    | gttttatcga gtataagtta acagaaaaag taaattaagc tttgccttta ctattttgaa   | 5282 |
|    | tttatataca ttctggaaaa acttagaaaac tgttgtatat ttcattagat taaattatat  | 5342 |
| 15 | gaaaatgtga ttgtttatag caaagcctgt gagttgcata caccctaagg aaaactcctt   | 5402 |
|    | aagtgctcct tgaagagaga agaaacaatt ctgggtcttg tctttttaag aacaaagcta   | 5462 |
|    | gactactgta tgtagcact gtacattaat agtctgttgt gaagcttgag cagtttcctg    | 5522 |
| 20 | catagccttg atccttcacc gttggcattg aaaatagcag tatccctgat gtacttaaaa   | 5582 |
|    | cttaaagtca ggttttggtg tattttatttg taagtcttaa tttcctctaa atactatata  | 5642 |
|    | tcttttagcg gacaacctga aattttattag cacatttggg tatctcttgc ttggcattat  | 5702 |
| 25 | ggccagtgtt aactattcag tggtgaaaaa attaccctc aagacactgg agtgaccca     | 5762 |
|    | gatgtgtgta gtaagtggca tggttcaact gtgtgggttaa tgataaatat atgacttagt  | 5822 |
| 30 | cggatatgatc tggaaagact tgattgaaag ataattcagc tgacataagg atgagtgagg  | 5882 |
|    | agtggcaaac tggataaaaag agtcaagaga cctgtattcc agtgactcct gttttgttta  | 5942 |
|    | agcattagca agatctgtct ggggaaactg gatagggcag ttttcttcca tgtttagttt   | 6002 |
| 35 | ttgtctcaac atttggaagc tattgaaggt tttaaaatgg tgtgtattgt ttttttttgg   | 6062 |
|    | gggggggggtg gccagaatag tgggtcatct aataaaaactg ccatttaaaa gatcaaaaaa | 6122 |
| 40 | aaaaaaaaa aaaaaaaaaa                                                | 6141 |

<210> 22

<211> 707

<212> PRT

<213> Mus musculus

<400> 22

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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly  
1 5 10 15

5 Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala  
20 25 30

10 Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln  
35 40 45

15 Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg  
50 55 60

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45

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu | Arg | Met |  |
|    | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 5  | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val | Ser | Lys |  |
|    |     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 10 | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu | Gln | Arg |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 15 | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr |  |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| 20 | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu |  |
|    | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 25 | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp |  |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| 30 | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser | Gly | Val | Pro | Ile | Leu |  |
|    |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     |     | 175 |     |  |
| 35 | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Val | Asp |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| 40 | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| 45 | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys |  |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 50 | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 55 | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu |  |
|    |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     |     | 255 |     |  |
| 60 | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 65 | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 70 | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser |  |
|    | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| 75 | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
| 5  | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ser | Asp | Pro | Leu | Val |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
|    | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr |  |
| 10 |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
|    | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp |  |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
| 15 | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp |  |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
|    | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val | His | Ser | Glu | Ser | Arg | Leu | Ala |  |
| 20 |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
|    | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
| 25 | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln |  |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
|    | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Met | Asp | Gln |  |
| 30 |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
|    | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
| 35 | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser |  |
|    |     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
|    | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln |  |
| 40 |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |
|    | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Ala | Asn |  |
| 45 |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
|    | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Ser | Gln | Tyr | Gln | Ala | Thr | Tyr | Asn |  |
|    |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |
| 50 | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Gln |  |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |
|    | Gln | Asp | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp |  |
| 55 |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     |     | 575 |     |  |
|    | Gln | Pro | His | Gln | Val | Pro | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn |  |

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|    | 580                                                             |     | 585 |     | 590 |
|----|-----------------------------------------------------------------|-----|-----|-----|-----|
| 5  | Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val | 595 | 600 | 605 |     |
| 10 | Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg | 610 | 615 | 620 |     |
| 15 | Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser | 625 | 630 | 635 | 640 |
| 20 | Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala | 645 | 650 | 655 |     |
| 25 | Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe | 660 | 665 | 670 |     |
| 30 | Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg | 675 | 680 | 685 |     |
| 35 | Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln | 690 | 695 | 700 |     |
| 40 | Gln Val Asn                                                     | 705 |     |     |     |

<210> 23  
 <211> 6114  
 <212> DNA  
 <213> Mus musculus

<220>  
 <221> CDS  
 <222> (139)..(2235)  
 <223>

<400> 23

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|    |                                                                                                                                                |     |
|----|------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|    | cccaccgcgc gcgcgcgtag ccgcctgccc gcccgcgcgc tgcgcgtttt gtcccgcgtc                                                                              | 60  |
|    | tctccccgtc cgtctcctga cttgctggtc ttgtccttcc ctcccgcgtt tttcctctcc                                                                              | 120 |
| 5  | tctctttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc<br>Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly<br>1 5 10                      | 171 |
| 10 | agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag<br>Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu<br>15 20 25 | 219 |
| 15 | gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc<br>Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly<br>30 35 40 | 267 |
| 20 | acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc<br>Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile<br>45 50 55 | 315 |
| 25 |                                                                                                                                                |     |
| 30 |                                                                                                                                                |     |
| 35 |                                                                                                                                                |     |
| 40 |                                                                                                                                                |     |
| 45 |                                                                                                                                                |     |
| 50 |                                                                                                                                                |     |
| 55 |                                                                                                                                                |     |

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|    |  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|--|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    |  | gac | aag | aaa | ctt | cgg | aac | ctg | gag | aag | aaa | aag | ggt | aaa | ctt | gat | gat | 363  |
|    |  | Asp | Lys | Lys | Leu | Arg | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp |      |
|    |  | 60  |     |     |     |     | 65  |     |     |     |     | 70  |     |     |     | 75  |     |      |
| 5  |  | tac | cag | gaa | cga | atg | aat | aaa | ggg | gaa | agg | ctc | aat | caa | gac | cag | ctg | 411  |
|    |  | Tyr | Gln | Glu | Arg | Met | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu |      |
|    |  |     |     |     |     | 80  |     |     |     |     | 85  |     |     |     |     | 90  |     |      |
|    |  | gat | gcc | gta | tct | aag | tac | cag | gaa | gtc | aca | aat | aat | ttg | gag | ttt | gca | 459  |
| 10 |  | Asp | Ala | Val | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala |      |
|    |  |     |     |     | 95  |     |     |     |     | 100 |     |     |     |     | 105 |     |     |      |
|    |  | aag | gaa | tta | cag | agg | agt | ttc | atg | gca | tta | agt | caa | gat | att | cag | aaa | 507  |
|    |  | Lys | Glu | Leu | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys |      |
|    |  |     |     | 110 |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |      |
| 15 |  | aca | ata | aag | aag | aca | gca | cgt | cgg | gaa | cag | ctt | atg | aga | gaa | gaa | gca | 555  |
|    |  | Thr | Ile | Lys | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala |      |
|    |  |     |     | 125 |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |      |
|    |  | gaa | cag | aag | cgc | tta | aaa | act | gta | ctt | gag | tta | cag | tat | gta | ttg | gat | 603  |
| 20 |  | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp |      |
|    |  | 140 |     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |      |
|    |  | aag | ctg | gga | gat | gat | gat | gtg | aga | aca | gat | ctg | aaa | caa | ggt | ttg | agt | 651  |
|    |  | Lys | Leu | Gly | Asp | Asp | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser |      |
| 25 |  |     |     |     |     | 160 |     |     |     |     | 165 |     |     |     |     | 170 |     |      |
|    |  | gga | gtg | cca | ata | ttg | tct | gag | gag | gag | ttg | tca | ttg | ctg | gat | gag | ttc | 699  |
|    |  | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe |      |
|    |  |     |     |     | 175 |     |     |     |     | 180 |     |     |     |     | 185 |     |     |      |
|    |  | tac | aag | ctc | gta | gat | cct | gag | cgt | gac | atg | agt | tta | agg | tta | aat | gag | 747  |
| 30 |  | Tyr | Lys | Leu | Val | Asp | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu |      |
|    |  |     |     | 190 |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |      |
|    |  | cag | tat | gaa | cat | gcc | tca | att | cac | ttg | tgg | gat | ttg | ctg | gaa | ggg | aaa | 795  |
| 35 |  | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys |      |
|    |  |     | 205 |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     |      |
|    |  | gaa | aag | cct | gtg | tgt | gga | aca | acc | tat | aaa | gct | cta | aag | gaa | att | gtt | 843  |
|    |  | Glu | Lys | Pro | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val |      |
|    |  | 220 |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |      |
| 40 |  | gag | cgt | gtt | ttc | cag | tca | aac | tac | ttt | gat | agc | act | cac | aat | cat | caa | 891  |
|    |  | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln |      |
|    |  |     |     |     | 240 |     |     |     |     |     | 245 |     |     |     |     | 250 |     |      |
|    |  | aat | ggg | ttg | tgt | gag | gag | gaa | gag | gcg | gct | tca | gcg | ccc | aca | gtg | gag | 939  |
| 45 |  | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu |      |
|    |  |     |     |     | 255 |     |     |     |     | 260 |     |     |     |     | 265 |     |     |      |
|    |  | gac | cag | gta | gct | gaa | gct | gaa | cct | gag | cca | gcg | gaa | gaa | tac | aca | gag | 987  |
|    |  | Asp | Gln | Val | Ala | Glu | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu |      |
| 50 |  |     |     | 270 |     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |      |
|    |  | caa | agt | gag | gtt | gaa | tca | aca | gag | tat | gtc | aat | agg | cag | ttc | atg | gca | 1035 |
|    |  | Gln | Ser | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala |      |
|    |  |     |     | 285 |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     |      |
| 55 |  | gaa | aca | cag | ttc | agc | agt | ggg | gag | aag | gag | caa | gtg | gat | gag | tgg | aca | 1083 |
|    |  | Glu | Thr | Gln | Phe | Ser | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr |      |
|    |  | 300 |     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |      |

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|    |                                                                 |      |
|----|-----------------------------------------------------------------|------|
|    | gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct | 1131 |
|    | Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala |      |
|    | 320 325 330                                                     |      |
| 5  | gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag | 1179 |
|    | Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln |      |
|    | 335 340 345                                                     |      |
| 10 | tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa | 1227 |
|    | Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln |      |
|    | 350 355 360                                                     |      |
|    | atg caa ggg ccc tat aat ttc ata cag acg ctt gat cct gcc att gta | 1275 |
|    | Met Gln Gly Pro Tyr Asn Phe Ile Gln Thr Leu Asp Pro Ala Ile Val |      |
|    | 365 370 375                                                     |      |
| 15 | tcc gca cag cct atg aac cct acc cag aac atg gat atg cct cag ctg | 1323 |
|    | Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu |      |
|    | 380 385 390 395                                                 |      |
| 20 | gtt tgc cct cag gtt cat tct gaa tct aga ctt gcc caa tct aat caa | 1371 |
|    | Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala Gln Ser Asn Gln |      |
|    | 400 405 410                                                     |      |
|    | gtt cct gta caa cca gaa gcc aca cag gtt cct ttg gtt tca tcc aca | 1419 |
|    | Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr |      |
|    | 415 420 425                                                     |      |
| 25 | agt gag ggg tat aca gca tct cag ccc ttg tac cag cca tct cat gct | 1467 |
|    | Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala |      |
|    | 430 435 440                                                     |      |
| 30 | acg gag cag cgg ccg cag aaa gag cca atg gat cag att cag gca aca | 1515 |
|    | Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln Ile Gln Ala Thr |      |
|    | 445 450 455                                                     |      |
|    | ata tct ttg aat aca gac cag act aca gca tcc tca tcc ctt cct gct | 1563 |
|    | Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala |      |
|    | 460 465 470 475                                                 |      |
| 35 | gct tct cag cct caa gtg ttc cag gct ggg aca agt aaa cct ttg cac | 1611 |
|    | Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His |      |
|    | 480 485 490                                                     |      |
| 40 | agc agt gga atc aat gta aat gca gct cca ttc cag tcc atg caa acg | 1659 |
|    | Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr |      |
|    | 495 500 505                                                     |      |
|    | gtg ttc aat atg aat gct cca gtc cct cct gct aat gaa cca gaa acg | 1707 |
|    | Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn Glu Pro Glu Thr |      |
|    | 510 515 520                                                     |      |
| 45 | tta aaa caa cag agt cag tac cag gcc act tat aac cag agt ttt tcc | 1755 |
|    | Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn Gln Ser Phe Ser |      |
|    | 525 530 535                                                     |      |
| 50 | agt cag cct cac caa gtg gaa caa aca gag ctt caa caa gac caa ctg | 1803 |
|    | Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln Gln Asp Gln Leu |      |
|    | 540 545 550 555                                                 |      |
|    | caa acg gtg gtt ggc act tac cat gga tcc cag gac cag cct cat caa | 1851 |
|    | Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln |      |
|    | 560 565 570                                                     |      |
| 55 | gtg cct ggt aac cac cag caa ccc cca cag cag aac act ggc ttt cca | 1899 |

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|    |            |            |            |             |              |             |     |     |     |     |     |     |     |     |     |     |      |
|----|------------|------------|------------|-------------|--------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Val        | Pro        | Gly        | Asn         | His          | Gln         | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro |      |
|    |            |            |            | 575         |              |             |     |     | 580 |     |     |     |     | 585 |     |     |      |
| 5  | cgt        | agc        | agt        | cag         | cct          | tat         | tac | aac | agt | cgt | ggg | gta | tct | cga | gga | ggg | 1947 |
|    | Arg        | Ser        | Ser        | Gln         | Pro          | Tyr         | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly |      |
|    |            |            |            | 590         |              |             |     | 595 |     |     |     |     | 600 |     |     |     |      |
| 10 | tct        | cgt        | ggg        | gcc         | aga          | ggc         | ttg | atg | aat | gga | tac | agg | ggc | cct | gcc | aat | 1995 |
|    | Ser        | Arg        | Gly        | Ala         | Arg          | Gly         | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn |      |
|    |            |            |            | 605         |              |             | 610 |     |     |     |     | 615 |     |     |     |     |      |
|    | gga        | ttt        | aga        | gga         | gga          | tat         | gat | ggg | tac | cgc | cct | tca | ttc | tcg | aac | act | 2043 |
|    | Gly        | Phe        | Arg        | Gly         | Gly          | Tyr         | Asp | Gly | Tyr | Arg | Pro | Ser | Phe | Ser | Asn | Thr |      |
|    |            |            |            |             |              | 625         |     |     |     |     | 630 |     |     |     |     | 635 |      |
| 15 | cca        | aac        | agt        | ggg         | tat          | tca         | cag | tct | cag | ttc | act | gct | ccc | cgg | gac | tac | 2091 |
|    | Pro        | Asn        | Ser        | Gly         | Tyr          | Ser         | Gln | Ser | Gln | Phe | Thr | Ala | Pro | Arg | Asp | Tyr |      |
|    |            |            |            |             | 640          |             |     |     |     | 645 |     |     |     |     | 650 |     |      |
| 20 | tct        | ggg        | tac        | cag         | cgg          | gat         | gga | tat | cag | cag | aat | ttc | aag | cga | ggc | tct | 2139 |
|    | Ser        | Gly        | Tyr        | Gln         | Arg          | Asp         | Gly | Tyr | Gln | Gln | Asn | Phe | Lys | Arg | Gly | Ser |      |
|    |            |            |            | 655         |              |             |     |     | 660 |     |     |     |     | 665 |     |     |      |
|    | ggg        | cag        | agt        | gga         | cca          | cgg         | gga | gcc | cca | cga | ggg | cgt | gga | ggg | ccc | cca | 2187 |
|    | Gly        | Gln        | Ser        | Gly         | Pro          | Arg         | Gly | Ala | Pro | Arg | Gly | Arg | Gly | Gly | Pro | Pro |      |
|    |            |            |            | 670         |              |             |     | 675 |     |     |     |     | 680 |     |     |     |      |
| 25 | aga        | ccc        | aac        | aga         | ggg          | atg         | ccg | caa | atg | aac | act | cag | caa | gtg | aat | taa | 2235 |
|    | Arg        | Pro        | Asn        | Arg         | Gly          | Met         | Pro | Gln | Met | Asn | Thr | Gln | Gln | Val | Asn |     |      |
|    |            |            |            | 685         |              |             | 690 |     |     |     |     | 695 |     |     |     |     |      |
| 30 | tgtgatacac | aggattatgt | ttaatcgcca | aaaacacact  | ggccagtgtgta | ccataatatg  |     |     |     |     |     |     |     |     |     |     | 2295 |
|    | ttaccagaag | agttattatc | tatttggtct | ccctttcagg  | aaacttattg   | taaaggggact |     |     |     |     |     |     |     |     |     |     | 2355 |
|    | gttttcatcc | cataaagaca | ggactgcaat | tgtcagcttt  | acattacctg   | gatatggaag  |     |     |     |     |     |     |     |     |     |     | 2415 |
| 35 | gaaactat   | ttattctgca | tggtctgtcc | taagcgtcat  | cttgagcctt   | gcacacaata  |     |     |     |     |     |     |     |     |     |     | 2475 |
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|    | atatctocat | agttagtga  | agtggtcttg | aaaaaaaatg  | caagattgaa   | tttttgacct  |     |     |     |     |     |     |     |     |     |     | 2595 |
| 40 | tggataaaat | ctacaatcag | ccctagaact | attcagtggt  | aattgacaaa   | gttaaagcat  |     |     |     |     |     |     |     |     |     |     | 2655 |
|    | tttctttgaa | aggaagatgg | aaggagtggg | gtgtggttta  | gcaaaactgc   | atttcatagc  |     |     |     |     |     |     |     |     |     |     | 2715 |
|    | tttcccatta | aattggagca | ccgacagatt | aaaagcatac  | caaattatgc   | atgggtcctt  |     |     |     |     |     |     |     |     |     |     | 2775 |
| 45 | actcacacaa | gtgaggctgg | ctaccagcct | tgacatagca  | ctcactagtc   | ttctggccaa  |     |     |     |     |     |     |     |     |     |     | 2835 |
|    | acgactgtga | ttaaaacaca | tgtaaattgc | tcttttagtag | tggatactgt   | gtaagacaaa  |     |     |     |     |     |     |     |     |     |     | 2895 |
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| 50 | ataatctgga | tgggctgctg | ctgtgctcaa | tgtgaactat  | ttagatacct   | ttggaacact  |     |     |     |     |     |     |     |     |     |     | 3015 |
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|    |             |             |             |             |             |             |      |
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| 15 | ccacttggtg  | acacaaaggc  | taagttaatg  | ttattttctg  | tacagaaatt  | aaattttact  | 3795 |
|    | tttagccttt  | tgtaaacttt  | tttttttttt  | ttccaagccg  | gtatcagcta  | ctcaaaacaa  | 3855 |
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|    | gcttcaatgt  | ttatttttaa  | ataaataaaa  | taagtctctg  | acttttctca  | tgtgtgggtta | 4035 |
|    | tggtacatca  | tattggaagg  | gttatctgtt  | tacttttgcc  | aagactattt  | tgccagcacc  | 4095 |
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|    | atatttattgg | gatggataaa  | atgtttgtgg  | tttattggat  | aatccctaga  | tggtgtgtta  | 4215 |
|    | cgtgtgtaga  | atataatttt  | atgatagtaa  | gaaagcaaaa  | ttgaagaaaa  | taagtttagt  | 4275 |
| 30 | attgaatttg  | agttctgaag  | tgaattcagg  | gaatgtctca  | cgtttcgggc  | ttctacccaa  | 4335 |
|    | agtgtagggc  | agaagggtga  | aaagttgttt  | gtagtttgac  | ttgtttattt  | tttaagttgc  | 4395 |
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| 45 | attttttttc  | atcctttctc  | ctcttttgat  | cattgtatct  | tgatattaaa  | aacatgacct  | 4875 |
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|    |                                                                    |      |
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|    | tttcctctaa atactatatc tcttttagcga gacaacctga aatttattag cacatttggg | 5655 |
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|    | aagacactgg agtgaccca gatgtgtgta gtaagtggca tggttcaact gtgtgggtaa   | 5775 |
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| 25 | ttttcttcca tgtttagttt ttgtctcaac atttggaagc tattgaaggt tttaaaatgg  | 6015 |
|    | tgtgtattgt ttttttttgg ggggggggtg gccagaatag tgggtcatct aataaaactg  | 6075 |
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|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Met | Pro | Ser | Ala | Thr | Ser | His | Ser | Gly | Ser | Gly | Ser | Lys | Ser | Ser | Gly |  |
|    | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 5  | Pro | Pro | Pro | Pro | Ser | Gly | Ser | Ser | Gly | Ser | Glu | Ala | Ala | Ala | Gly | Ala |  |
|    |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
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|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 15 | Thr | Glu | Ala | Met | Lys | Gln | Ile | Leu | Gly | Val | Ile | Asp | Lys | Lys | Leu | Arg |  |
|    |     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu | Arg | Met |  |
|    | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 25 | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val | Ser | Lys |  |
|    |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 30 | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu | Gln | Arg |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 35 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 40 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 50 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| 5  | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu |
|    |     |     | 130 |     |     |     | 135 |     |     |     |     |     | 140 |     |     |     |
| 10 | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     | 160 |     |
| 15 | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser | Gly | Val | Pro | Ile | Leu |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |
| 20 | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Val | Asp |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |
| 25 | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |
| 30 | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys |
|    | 210 |     |     |     |     | 215 |     |     |     |     |     | 220 |     |     |     |     |
| 35 | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |
| 40 | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |
| 45 | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |
| 50 | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| 55 | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser |
|    | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| 60 | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| 65 | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| 70 | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ser | Asp | Pro | Leu | Val |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| 75 | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Asn | Phe | Ile | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met |  |
|    | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
| 5  | Asn | Pro | Thr | Gln | Asn | Met | Asp | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val |  |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
| 10 | His | Ser | Glu | Ser | Arg | Leu | Ala | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro |  |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| 15 | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
| 20 | Ala | Ser | Gln | Pro | Leu | Tyr | Gln | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro |  |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
| 25 | Gln | Lys | Glu | Pro | Met | Asp | Gln | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr |  |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| 30 | Asp | Gln | Thr | Thr | Ala | Ser | Ser | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
| 35 | Val | Phe | Gln | Ala | Gly | Thr | Ser | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn |  |
|    |     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
| 40 | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn |  |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |
| 45 | Ala | Pro | Val | Pro | Pro | Ala | Asn | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Ser |  |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
| 50 | Gln | Tyr | Gln | Ala | Thr | Tyr | Asn | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln |  |
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| 55 | Val | Glu | Gln | Thr | Glu | Leu | Gln | Gln | Asp | Gln | Leu | Gln | Thr | Val | Val | Gly |  |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |
| 60 | Thr | Tyr | His | Gly | Ser | Gln | Asp | Gln | Pro | His | Gln | Val | Pro | Gly | Asn | His |  |
|    |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |  |
| 65 | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg | Ser | Ser | Gln | Pro |  |
|    |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |
| 70 | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg |  |
|    |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
| 75 | Gly | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly |  |
|    |     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |

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5 Ser Gln Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg  
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10 Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro  
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| 5  | ccacccttgc cccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg     | 178 |
|    | atg ccc tcg gcc acc agc cac agc gga agc ggc agc aaa tcg tcg gga    | 226 |
|    | Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly    |     |
|    | 1 5 10 15                                                          |     |
| 10 | ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag gcg gcg gcc ggg gca    | 274 |
|    | Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala    |     |
|    | 20 25 30                                                           |     |
| 15 | gct gcg ccg gct tct cag cat ccg gca acc ggc acc ggc gcc gtc cag    | 322 |
|    | Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln    |     |
|    | 35 40 45                                                           |     |
| 20 | acc gag gcc atg aag cag att ctc ggc gta atc gac aag aaa ctt cgg    | 370 |
|    | Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg    |     |
|    | 50 55 60                                                           |     |
| 25 | aac ctg gag aag aaa aag ggt aaa ctt gat gat tac cag gaa cga atg    | 418 |
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|    | 65 70 75 80                                                        |     |
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|    | Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys    |     |
|    | 85 90 95                                                           |     |
| 35 | tac cag gaa gtc aca aat aat ttg gag ttt gca aag gaa tta cag agg    | 514 |
|    | Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg    |     |
|    | 100 105 110                                                        |     |

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|    |                                                                 |      |
|----|-----------------------------------------------------------------|------|
|    | agt ttc atg gca tta agt caa gat att cag aaa aca ata aag aag aca | 562  |
|    | Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr |      |
|    | 115 120 125                                                     |      |
| 5  | gca cgt cgg gaa cag ctt atg aga gaa gaa gca gaa cag aag cgc tta | 610  |
|    | Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu |      |
|    | 130 135 140                                                     |      |
| 10 | aaa act gta ctt gag tta cag tat gta ttg gat aag ctg gga gat gat | 658  |
|    | Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp |      |
|    | 145 150 155 160                                                 |      |
|    | gat gtg aga aca gat ctg aaa caa ggt ttg agt gga gtg cca ata ttg | 706  |
|    | Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu |      |
|    | 165 170 175                                                     |      |
| 15 | tct gag gag gag ttg tca ttg ctg gat gag ttc tac aag ctc gta gat | 754  |
|    | Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp |      |
|    | 180 185 190                                                     |      |
| 20 | cct gag cgt gac atg agt tta agg tta aat gag cag tat gaa cat gcc | 802  |
|    | Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala |      |
|    | 195 200 205                                                     |      |
|    | tca att cac ttg tgg gat ttg ctg gaa ggg aaa gaa aag cct gtg tgt | 850  |
|    | Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys |      |
|    | 210 215 220                                                     |      |
| 25 | gga aca acc tat aaa gct cta aag gaa att gtt gag cgt gtt ttc cag | 898  |
|    | Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln |      |
|    | 225 230 235 240                                                 |      |
| 30 | tca aac tac ttt gat agc act cac aat cat caa aat ggg ttg tgt gag | 946  |
|    | Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu |      |
|    | 245 250 255                                                     |      |
|    | gag gaa gag gcg gct tca gcg ccc aca gtg gag gac cag gta gct gaa | 994  |
|    | Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu |      |
|    | 260 265 270                                                     |      |
| 35 | gct gaa cct gag cca gcg gaa gaa tac aca gag caa agt gag gtt gaa | 1042 |
|    | Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu |      |
|    | 275 280 285                                                     |      |
| 40 | tca aca gag tat gtc aat agg cag ttc atg gca gaa aca cag ttc agc | 1090 |
|    | Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser |      |
|    | 290 295 300                                                     |      |
| 45 | agt ggt gag aag gag caa gtg gat gag tgg aca gtt gaa aca gtt gag | 1138 |
|    | Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu |      |
|    | 305 310 315 320                                                 |      |
|    | gtt gta aac tca ctc cag cag caa cct cag gct gcg tcc cct tca gtc | 1186 |
|    | Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val |      |
|    | 325 330 335                                                     |      |
| 50 | cca gag ccc cac tct ttg act cca gtg gct cag tca gat cca ctt gtg | 1234 |
|    | Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val |      |
|    | 340 345 350                                                     |      |
| 55 | aga agg cag cgt gta caa gat ctt atg gca caa atg caa ggg ccc tat | 1282 |
|    | Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr |      |
|    | 355 360 365                                                     |      |
|    | aat ttc ata cag gat tca atg ttg gat ttt gaa aat cag acg ctt gat | 1330 |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp |      |
|    | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |      |
| 5  | cct | gcc | att | gta | tcc | gca | cag | cct | atg | aac | cct | acc | cag | aac | atg | gat | 1378 |
|    | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp |      |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |      |
|    | atg | cct | cag | ctg | gtt | tgc | cct | cag | gtt | cat | tct | gaa | tct | aga | ctt | gcc | 1426 |
|    | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val | His | Ser | Glu | Ser | Arg | Leu | Ala |      |
| 10 |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |      |
|    | caa | tct | aat | caa | gtt | cct | gta | caa | cca | gaa | gcc | aca | cag | gtt | cct | ttg | 1474 |
|    | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu |      |
|    |     |     |     | 420 |     |     |     | 425 |     |     |     |     |     | 430 |     |     |      |
| 15 | gtt | tca | tcc | aca | agt | gag | ggg | tat | aca | gca | tct | cag | ccc | ttg | tac | cag | 1522 |
|    | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln |      |
|    |     |     | 435 |     |     |     | 440 |     |     |     |     | 445 |     |     |     |     |      |
|    | cca | tct | cat | gct | acg | gag | cag | cgg | ccg | cag | aaa | gag | cca | atg | gat | cag | 1570 |
|    | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Met | Asp | Gln |      |
| 20 |     | 450 |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |     |      |
|    | att | cag | gca | aca | ata | tct | ttg | aat | aca | gac | cag | act | aca | gca | tcc | tca | 1618 |
|    | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser |      |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |      |
| 25 | tcc | ctt | cct | gct | gct | tct | cag | cct | caa | gtg | ttc | cag | gct | ggg | aca | agt | 1666 |
|    | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser |      |
|    |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |     |      |
|    | aaa | cct | ttg | cac | agc | agt | gga | atc | aat | gta | aat | gca | gct | cca | ttc | cag | 1714 |
|    | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln |      |
| 30 |     |     |     | 500 |     |     |     | 505 |     |     |     |     |     | 510 |     |     |      |
|    | tcc | atg | caa | acg | gtg | ttc | aat | atg | aat | gct | cca | gtc | cct | cct | gct | aat | 1762 |
|    | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Ala | Asn |      |
|    |     |     | 515 |     |     |     | 520 |     |     |     |     |     | 525 |     |     |     |      |
| 35 | gaa | cca | gaa | acg | tta | aaa | caa | cag | agt | cag | tac | cag | gcc | act | tat | aac | 1810 |
|    | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Ser | Gln | Tyr | Gln | Ala | Thr | Tyr | Asn |      |
|    |     | 530 |     |     |     | 535 |     |     |     |     |     | 540 |     |     |     |     |      |
|    | cag | agt | ttt | tcc | agt | cag | cct | cac | caa | gtg | gaa | caa | aca | gag | ctt | caa | 1858 |
|    | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Gln |      |
| 40 | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |      |
|    | caa | gac | caa | ctg | caa | acg | gtg | gtt | ggc | act | tac | cat | gga | tcc | cag | gac | 1906 |
|    | Gln | Asp | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp |      |
|    |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |     |      |
| 45 | cag | cct | cat | caa | gtg | cct | ggc | aac | cac | cag | caa | ccc | cca | cag | cag | aac | 1954 |
|    | Gln | Pro | His | Gln | Val | Pro | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn |      |
|    |     |     |     | 580 |     |     |     | 585 |     |     |     |     |     | 590 |     |     |      |
|    | act | ggc | ttt | cca | cgt | agc | agt | cag | cct | tat | tac | aac | agt | cgt | ggg | gta | 2002 |
|    | Thr | Gly | Phe | Pro | Arg | Ser | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val |      |
| 50 |     |     | 595 |     |     |     | 600 |     |     |     |     |     | 605 |     |     |     |      |
|    | tct | cga | gga | ggg | tct | cgt | ggc | aga | ggc | ttg | atg | aat | gga | tac | agg |     | 2050 |
|    | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg |      |
|    |     | 610 |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |     |      |
| 55 | ggc | cct | gcc | aat | gga | ttt | aga | gga | gga | tat | gat | ggc | tac | cgc | cct | tca | 2098 |
|    | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser |      |

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|    | 625                                                                                                                                        | 630 | 635 | 640 |              |
|----|--------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|--------------|
| 5  | ttc tcg aac act cca aac agt ggt tat tca cag tct cag ttc act gct<br>Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala         | 645 | 650 | 655 | 2146         |
| 10 | ccc cgg gac tac tct ggt tac cag cgg gat gga tat cag cag aat ttc<br>Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe         | 660 | 665 | 670 | 2194         |
| 15 | aag cga ggc tct ggg cag agt gga cca cgg gga gcc cca cga ggt aat<br>Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn         | 675 | 680 | 685 | 2242         |
| 20 | ata ttg tgg tgg tga tcctagctcc tatgtggagc ttctgttctg gccttggaag<br>Ile Leu Trp Trp                                                         | 690 |     |     | 2297         |
| 25 | aactgttcat agtccgcatg taggttacat gttaggaata catttatctt ttccagactt<br>gttgctaaag attaaatgaa atgctctgtt tctaaaattt catcttgaat ccaaatttta     |     |     |     | 2357<br>2417 |
| 30 | atTTTTgaat gactttccct gctgttgtct tcaaaatcag aacattttct ctgcctcaga<br>aaagcgtttt tccaactgga aattttatttt tcaggtctta aaacctgcta aatgttttta    |     |     |     | 2477<br>2537 |
| 35 | ggaagtacct actgaaactt tttgtaagac atTTTTggaa cgagcttgaa catttatata<br>aatttattac cctctttgat ttttgaaaca tgcatattat atttaggctg agaagccctt     |     |     |     | 2597<br>2657 |
| 40 | caaagtggcca gataagccac agtttttagct agagaacccat ttagaattga cataactaat<br>ctaaacttga acacttttag gaccaatgtt agtggttctaa ataccaacat atttctgatg |     |     |     | 2717<br>2777 |
| 45 | tttaaacaga tctcccaaatt tcttaggacc ttgatgtcat taaaatttag aatgacaagc<br>ttaagaggct ttagtttcat ttgtttttca agtaatgaaa aataatttct tacatgggca    |     |     |     | 2837<br>2897 |
| 50 | gatagttaat ttgttgaaca attacaggta gcatttcatg taatctgatg ttctaaatgg<br>ttctcttatt gaaggagggtt aaagaatttag gtttcttaca gtttttggct ggccatgaca   |     |     |     | 2957<br>3017 |
| 55 | tgtataaaat gtatatataag gaggaattat aaagtacttt aatttgaatg ctagtggcaa<br>ttgatcatta agaaagtact ttaaagcaaa aggttaatgg gtcactctggg aaaaatactg   |     |     |     | 3077<br>3137 |
|    | aagtatcaaa ggtatttgca tgtgaatgtg ggttatgttc ttctatccca ccttgtagca<br>tattctatga aagttgagtt aaatgatagc taaaatatct gtttcaacag catgtaaaaa     |     |     |     | 3197<br>3257 |
|    | gttattttta ctgttacaag tcattataca attttgaatg ttctgtagtt tctttttaac<br>agtttaggta caaaggctctg ttttcattct ggtgcttttt attaatTTtg atagtatgat    |     |     |     | 3317<br>3377 |
|    | gtcacttcct attgaaatgt aagctagcgt gtaccttaga atgtgagctc catgagagca<br>ggtaccttgt ttgtcttcac tgctgtatct attcccaacg cctcatgaca gtgcctggca     |     |     |     | 3437<br>3497 |
|    | catagtaggc actcaataaa tacttggtga atgaatgaaa aaaaaaaaaa a                                                                                   |     |     |     | 3548         |

&lt;210&gt; 26

<211> 692  
<212> PRT  
<213> Mus musculus

5      <400> 26

10

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Met | Pro | Ser | Ala | Thr | Ser | His | Ser | Gly | Ser | Gly | Ser | Lys | Ser | Ser | Gly |  |
|    | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 5  | Pro | Pro | Pro | Pro | Ser | Gly | Ser | Ser | Gly | Ser | Glu | Ala | Ala | Ala | Gly | Ala |  |
|    |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Ala | Ala | Pro | Ala | Ser | Gln | His | Pro | Ala | Thr | Gly | Thr | Gly | Ala | Val | Gln |  |
|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 15 | Thr | Glu | Ala | Met | Lys | Gln | Ile | Leu | Gly | Val | Ile | Asp | Lys | Lys | Leu | Arg |  |
|    | 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp | Tyr | Gln | Glu | Arg | Met |  |
|    | 65  |     |     |     |     | 70  |     |     |     | 75  |     |     |     |     |     | 80  |  |
| 25 | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu | Asp | Ala | Val | Ser | Lys |  |
|    |     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 30 | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala | Lys | Glu | Leu | Gln | Arg |  |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 35 | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys | Thr | Ile | Lys | Lys | Thr |  |
|    |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| 40 | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala | Glu | Gln | Lys | Arg | Leu |  |
|    | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 45 | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp |  |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |
| 50 | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser | Gly | Val | Pro | Ile | Leu |  |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| 55 | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Val | Asp |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| 60 | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| 65 | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys |  |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 70 | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 75 | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu |  |
|    |     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 5  | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 10 | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser |  |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| 15 | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu |  |
|    | 305 |     |     |     |     | 310 |     |     |     | 315 |     |     |     |     |     | 320 |  |
| 20 | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val |  |
|    |     |     |     |     | 325 |     |     |     | 330 |     |     |     |     |     | 335 |     |  |
| 25 | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ser | Asp | Pro | Leu | Val |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |
| 30 | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
| 35 | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp |  |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
| 40 | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp |  |
|    |     | 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
| 45 | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val | His | Ser | Glu | Ser | Arg | Leu | Ala |  |
|    |     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| 50 | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
| 55 | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln |  |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
| 60 | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Met | Asp | Gln |  |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| 65 | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
| 70 | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser |  |
|    |     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
| 75 | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln |  |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |

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|    |       |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-------|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Ser   | Met           | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Ala | Asn |
|    |       |               | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| 5  | Glu   | Pro           | Glu | Thr | Leu | Lys | Gln | Gln | Ser | Gln | Tyr | Gln | Ala | Thr | Tyr | Asn |
|    |       | 530           |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| 10 | Gln   | Ser           | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Gln |
|    | 545   |               |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| 15 | Gln   | Asp           | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp |
|    |       |               |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |
| 20 | Gln   | Pro           | His | Gln | Val | Pro | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn |
|    |       |               |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| 25 | Thr   | Gly           | Phe | Pro | Arg | Ser | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val |
|    |       |               | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| 30 | Ser   | Arg           | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg |
|    | 610   |               |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| 35 | Gly   | Pro           | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser |
|    | 625   |               |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| 40 | Phe   | Ser           | Asn | Thr | Pro | Asn | Ser | Gly | Tyr | Ser | Gln | Ser | Gln | Phe | Thr | Ala |
|    |       |               |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |
| 45 | Pro   | Arg           | Asp | Tyr | Ser | Gly | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln | Asn | Phe |
|    |       |               |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |
| 50 | Lys   | Arg           | Gly | Ser | Gly | Gln | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg | Gly | Asn |
|    |       |               | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| 55 | Ile   | Leu           | Trp | Trp |     |     |     |     |     |     |     |     |     |     |     |     |
|    |       |               | 690 |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 55 | <210> | 27            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> | 3508          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> | DNA           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> | Mus musculus  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 50 | <220> |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <221> | CDS           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <222> | (139)..(2217) |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <223> |               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 55 | <400> | 27            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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|   |                                                                 |     |
|---|-----------------------------------------------------------------|-----|
|   | cccaccgcgc gcgcgcgtag ccgcctgcc gccgcgcgc tgccgcgttt gtccgcgcgc | 60  |
|   | tctcccgtc cgtctcctga ctgctggc ttgtccttc ctccgcgttt tttcctctcc   | 120 |
| 5 | tctcttctcg gtctaaag atg cc tcg gcc acc agc cac agc gga agc ggc  | 171 |

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|    |  |     |     |     |     | Met | Pro | Ser | Ala | Thr | Ser | His | Ser | Gly | Ser | Gly |     |     |
|----|--|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    |  |     |     |     |     | 1   |     |     |     | 5   |     |     |     |     |     | 10  |     |     |
| 5  |  | agc | aaa | tcg | tcg | gga | ccg | ccg | ccg | ccg | tcc | ggt | tcc | tcc | ggg | agt | gag | 219 |
|    |  | Ser | Lys | Ser | Ser | Gly | Pro | Pro | Pro | Pro | Ser | Gly | Ser | Ser | Gly | Ser | Glu |     |
|    |  |     |     |     | 15  |     |     |     |     | 20  |     |     |     |     | 25  |     |     |     |
| 10 |  | gcg | gcg | gcc | ggg | gca | gct | gcg | ccg | gct | tct | cag | cat | ccg | gca | acc | ggc | 267 |
|    |  | Ala | Ala | Ala | Gly | Ala | Ala | Ala | Pro | Ala | Ser | Gln | His | Pro | Ala | Thr | Gly |     |
|    |  |     |     | 30  |     |     |     |     | 35  |     |     |     |     | 40  |     |     |     |     |
| 15 |  | acc | ggc | gcc | gtc | cag | acc | gag | gcc | atg | aag | cag | att | ctc | ggc | gta | atc | 315 |
|    |  | Thr | Gly | Ala | Val | Gln | Thr | Glu | Ala | Met | Lys | Gln | Ile | Leu | Gly | Val | Ile |     |
|    |  |     | 45  |     |     |     |     | 50  |     |     |     |     | 55  |     |     |     |     |     |
| 20 |  | gac | aag | aaa | ctt | cgg | aac | ctg | gag | aag | aaa | aag | ggt | aaa | ctt | gat | gat | 363 |
|    |  | Asp | Lys | Lys | Leu | Arg | Asn | Leu | Glu | Lys | Lys | Lys | Gly | Lys | Leu | Asp | Asp |     |
|    |  | 60  |     |     |     |     | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |
| 25 |  | tac | cag | gaa | cga | atg | aat | aaa | ggg | gaa | agg | ctc | aat | caa | gac | cag | ctg | 411 |
|    |  | Tyr | Gln | Glu | Arg | Met | Asn | Lys | Gly | Glu | Arg | Leu | Asn | Gln | Asp | Gln | Leu |     |
|    |  |     |     |     | 80  |     |     |     |     |     | 85  |     |     |     |     | 90  |     |     |
| 30 |  | gat | gcc | gta | tct | aag | tac | cag | gaa | gtc | aca | aat | aat | ttg | gag | ttt | gca | 459 |
|    |  | Asp | Ala | Val | Ser | Lys | Tyr | Gln | Glu | Val | Thr | Asn | Asn | Leu | Glu | Phe | Ala |     |
|    |  |     |     |     | 95  |     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |
| 35 |  | aag | gaa | tta | cag | agg | agt | ttc | atg | gca | tta | agt | caa | gat | att | cag | aaa | 507 |
|    |  | Lys | Glu | Leu | Gln | Arg | Ser | Phe | Met | Ala | Leu | Ser | Gln | Asp | Ile | Gln | Lys |     |
|    |  |     |     | 110 |     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     |
| 40 |  | aca | ata | aag | aag | aca | gca | cgt | cgg | gaa | cag | ctt | atg | aga | gaa | gaa | gca | 555 |
|    |  | Thr | Ile | Lys | Lys | Thr | Ala | Arg | Arg | Glu | Gln | Leu | Met | Arg | Glu | Glu | Ala |     |
|    |  |     | 125 |     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     |     |
| 45 |  | gaa | cag | aag | cgc | tta | aaa | act | gta | ctt | gag | tta | cag | tat | gta | ttg | gat | 603 |
|    |  | Glu | Gln | Lys | Arg | Leu | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp |     |
|    |  | 140 |     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |
| 50 |  | aag | ctg | gga | gat | gat | gat | gtg | aga | aca | gat | ctg | aaa | caa | ggt | ttg | agt | 651 |
|    |  | Lys | Leu | Gly | Asp | Asp | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser |     |
|    |  |     |     |     | 160 |     |     |     |     |     | 165 |     |     |     |     | 170 |     |     |
| 55 |  | gga | gtg | cca | ata | ttg | tct | gag | gag | gag | ttg | tca | ttg | ctg | gat | gag | ttc | 699 |
|    |  | Gly | Val | Pro | Ile | Leu | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe |     |
|    |  |     |     |     | 175 |     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |
| 60 |  | tac | aag | ctc | gta | gat | cct | gag | cgt | gac | atg | agt | tta | agg | tta | aat | gag | 747 |
|    |  | Tyr | Lys | Leu | Val | Asp | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu |     |
|    |  |     |     | 190 |     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     |
| 65 |  | cag | tat | gaa | cat | gcc | tca | att | cac | ttg | tgg | gat | ttg | ctg | gaa | ggg | aaa | 795 |
|    |  | Gln | Tyr | Glu | His | Ala | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys |     |
|    |  |     | 205 |     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     |     |
| 70 |  | gaa | aag | cct | gtg | tgt | gga | aca | acc | tat | aaa | gct | cta | aag | gaa | att | gtt | 843 |
|    |  | Glu | Lys | Pro | Val | Cys | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val |     |
|    |  | 220 |     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |
| 75 |  | gag | cgt | gtt | ttc | cag | tca | aac | tac | ttt | gat | agc | act | cac | aat | cat | caa | 891 |
|    |  | Glu | Arg | Val | Phe | Gln | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln |     |
|    |  |     |     |     | 240 |     |     |     |     |     | 245 |     |     |     |     | 250 |     |     |
| 80 |  | aat | ggg | ttg | tgt | gag | gag | gaa | gag | gcg | gct | tca | gcg | ccc | aca | gtg | gag | 939 |
|    |  | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu |     |

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|    | 255                                                                                                                                                   | 260 | 265 |      |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|-----|------|
| 5  | gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag<br>Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu<br>270 275 280     |     |     | 987  |
|    | caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca<br>Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala<br>285 290 295     |     |     | 1035 |
| 10 | gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca<br>Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr<br>300 305 310 315 |     |     | 1083 |
| 15 | gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct<br>Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala<br>320 325 330     |     |     | 1131 |
|    | gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag<br>Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln<br>335 340 345     |     |     | 1179 |
| 20 | tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa<br>Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln<br>350 355 360     |     |     | 1227 |
| 25 | atg caa ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt gaa<br>Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu<br>365 370 375     |     |     | 1275 |
|    | aat cag acg ctt gat cct gcc att gta tcc gca cag cct atg aac cct<br>Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro<br>380 385 390 395 |     |     | 1323 |
| 30 | acc cag aac atg gat atg cct cag ctg gtt tgc cct cag gtt cat tct<br>Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val His Ser<br>400 405 410     |     |     | 1371 |
| 35 | gaa tct aga ctt gcc caa tct aat caa gtt cct gta caa cca gaa gcc<br>Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala<br>415 420 425     |     |     | 1419 |
|    | aca cag gtt cct ttg gtt tca tcc aca agt gag ggg tat aca gca tct<br>Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser<br>430 435 440     |     |     | 1467 |
| 40 | cag ccc ttg tac cag cca tct cat gct acg gag cag cgg ccg cag aaa<br>Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys<br>445 450 455     |     |     | 1515 |
| 45 | gag cca atg gat cag att cag gca aca ata tct ttg aat aca gac cag<br>Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln<br>460 465 470 475 |     |     | 1563 |
|    | act aca gca tcc tca tcc ctt cct gct gct tct cag cct caa gtg ttc<br>Thr Thr Ala Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe<br>480 485 490         |     |     | 1611 |
| 50 | cag gct ggg aca agt aaa cct ttg cac agc agt gga atc aat gta aat<br>Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn<br>495 500 505     |     |     | 1659 |
| 55 | gca gct cca ttc cag tcc atg caa acg gtg ttc aat atg aat gct cca<br>Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro<br>510 515 520     |     |     | 1707 |

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|    |                                                                    |      |
|----|--------------------------------------------------------------------|------|
|    | gtc cct cct gct aat gaa cca gaa acg tta aaa caa cag agt cag tac    | 1755 |
|    | Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr    |      |
|    | 525 530 535                                                        |      |
| 5  | cag gcc act tat aac cag agt ttt tcc agt cag cct cac caa gtg gaa    | 1803 |
|    | Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu    |      |
|    | 540 545 550 555                                                    |      |
| 10 | caa aca gag ctt caa caa gac caa ctg caa acg gtg gtt ggc act tac    | 1851 |
|    | Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr    |      |
|    | 560 565 570                                                        |      |
| 15 | cat gga tcc cag gac cag cct cat caa gtg cct ggt aac cac cag caa    | 1899 |
|    | His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln    |      |
|    | 575 580 585                                                        |      |
| 20 | ccc cca cag cag aac act ggc ttt cca cgt agc agt cag cct tat tac    | 1947 |
|    | Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr    |      |
|    | 590 595 600                                                        |      |
| 25 | aac agt cgt ggg gta tct cga gga ggg tct cgt ggt gcc aga ggc ttg    | 1995 |
|    | Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu    |      |
|    | 605 610 615                                                        |      |
| 30 | atg aat gga tac agg ggc cct gcc aat gga ttt aga gga gga tat gat    | 2043 |
|    | Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp    |      |
|    | 620 625 630 635                                                    |      |
| 35 | ggt tac cgc cct tca ttc tcg aac act cca aac agt ggt tat tca cag    | 2091 |
|    | Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln    |      |
|    | 640 645 650                                                        |      |
| 40 | tct cag ttc act gct ccc cgg gac tac tct ggt tac cag cgg gat gga    | 2139 |
|    | Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly    |      |
|    | 655 660 665                                                        |      |
| 45 | tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga    | 2187 |
|    | Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly    |      |
|    | 670 675 680                                                        |      |
| 50 | gcc cca cga ggt aat ata ttg tgg tgg tga tcctagctcc tatgtggagc      | 2237 |
|    | Ala Pro Arg Gly Asn Ile Leu Trp Trp                                |      |
|    | 685 690                                                            |      |
| 55 | ttctgttctg gccttggaag aactgttcat agtccgcatg taggttacat gttaggaata  | 2297 |
|    | catttatctt ttccagactt gttgctaaag attaaatgaa atgctctgtt tctaaaattt  | 2357 |
|    | catcttgaat ccaaatttta atttttgaat gactttccct gctgttgtct tcaaaatcag  | 2417 |
|    | aacattttct ctgcctcaga aaagcgtttt tccaactgga aattttatttt tcaggtctta | 2477 |
|    | aaacctgcta aatgttttta ggaagtacct actgaaactt tttgtaagac atttttggaa  | 2537 |
|    | cgagcttgaa catttatata aatttattac cctctttgat ttttgaaaca tgcatattat  | 2597 |
|    | atttaggctg agaagccctt caaatggcca gataagccac agtttttagct agagaaccat | 2657 |
|    | ttagaattga cataactaat ctaaacttga acacttttag gaccaatgtt agtgttctaa  | 2717 |
|    | ataccaacat atttctgatg tttaaacaga tctcccaaatt tcttaggacc ttgatgtcat | 2777 |
|    | taaaatttag aatgacaagc ttaagaggct ttagtttcat ttgtttttca agtaatgaaa  | 2837 |

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|    |                                                                    |      |
|----|--------------------------------------------------------------------|------|
|    | aataatttct tacatgggca gatagttaat ttgttgaaca attacaggta gcatttcatg  | 2897 |
|    | taatctgatg ttctaaatgg ttctcttatt gaaggagggt aaagaattag gtttcttaca  | 2957 |
| 5  | gtttttggct ggccatgaca tgtataaaat gtatattaag gaggaattat aaagtacttt  | 3017 |
|    | aatttgaatg ctagtggcaa ttgatcatta agaaagtact ttaaagcaaa aggttaatgg  | 3077 |
|    | gtcatctggg aaaaatactg aagtatcaaa ggtatttgca tgtgaatgtg ggttatgttc  | 3137 |
| 10 | ttctatccca ccttgtagca tattctatga aagttgagtt aaatgatagc taaaatatct  | 3197 |
|    | gtttcaacag catgtaaaaa gttattttta ctgttacaag tcattataca attttgaatg  | 3257 |
|    | ttctgtagtt tctttttaac agtttaggta caaaggctctg ttttcattct ggtgcttttt | 3317 |
| 15 | attaattttg atagtatgat gtcacttcct attgaaatgt aagctagcgt gtaccttaga  | 3377 |
|    | atgtgagctc catgagagca ggtaccttgt ttgtcttcac tgctgtatct attcccaacg  | 3437 |
|    | cctcatgaca gtgcctggca catagtaggc actcaataaa tacttgttga atgaatgaaa  | 3497 |
| 20 | aaaaaaaaa a                                                        | 3508 |

<210> 28  
 <211> 692  
 <212> PRT  
 <213> Mus musculus

<400> 28

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

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|    | 130 |     | 135 |     | 140 |     |     |     |     |     |     |     |     |     |     |     |  |  |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|
| 5  | Lys | Thr | Val | Leu | Glu | Leu | Gln | Tyr | Val | Leu | Asp | Lys | Leu | Gly | Asp | Asp |  |  |  |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |  |  |  |
|    | Asp | Val | Arg | Thr | Asp | Leu | Lys | Gln | Gly | Leu | Ser | Gly | Val | Pro | Ile | Leu |  |  |  |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |  |  |
| 10 | Ser | Glu | Glu | Glu | Leu | Ser | Leu | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Val | Asp |  |  |  |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |  |  |
| 15 | Pro | Glu | Arg | Asp | Met | Ser | Leu | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | His | Ala |  |  |  |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |  |  |
|    | Ser | Ile | His | Leu | Trp | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys |  |  |  |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |  |  |
| 20 | Gly | Thr | Thr | Tyr | Lys | Ala | Leu | Lys | Glu | Ile | Val | Glu | Arg | Val | Phe | Gln |  |  |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |  |  |
| 25 | Ser | Asn | Tyr | Phe | Asp | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu |  |  |  |
|    |     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |  |  |
|    | Glu | Glu | Glu | Ala | Ala | Ser | Ala | Pro | Thr | Val | Glu | Asp | Gln | Val | Ala | Glu |  |  |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |  |  |
| 30 | Ala | Glu | Pro | Glu | Pro | Ala | Glu | Glu | Tyr | Thr | Glu | Gln | Ser | Glu | Val | Glu |  |  |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |  |  |
| 35 | Ser | Thr | Glu | Tyr | Val | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser |  |  |  |
|    | 290 |     |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |  |  |
|    | Ser | Gly | Glu | Lys | Glu | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu |  |  |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |  |  |
| 40 | Val | Val | Asn | Ser | Leu | Gln | Gln | Gln | Pro | Gln | Ala | Ala | Ser | Pro | Ser | Val |  |  |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |  |  |
| 45 | Pro | Glu | Pro | His | Ser | Leu | Thr | Pro | Val | Ala | Gln | Ser | Asp | Pro | Leu | Val |  |  |  |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |  |  |  |
|    | Arg | Arg | Gln | Arg | Val | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr |  |  |  |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |  |  |
| 50 | Asn | Phe | Ile | Gln | Asp | Ser | Met | Leu | Asp | Phe | Glu | Asn | Gln | Thr | Leu | Asp |  |  |  |
|    | 370 |     |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |  |  |
| 55 | Pro | Ala | Ile | Val | Ser | Ala | Gln | Pro | Met | Asn | Pro | Thr | Gln | Asn | Met | Asp |  |  |  |
|    | 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |  |  |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Met | Pro | Gln | Leu | Val | Cys | Pro | Gln | Val | His | Ser | Glu | Ser | Arg | Leu | Ala |  |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| 5  | Gln | Ser | Asn | Gln | Val | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
| 10 | Val | Ser | Ser | Thr | Ser | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Leu | Tyr | Gln |  |
|    |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
| 15 | Pro | Ser | His | Ala | Thr | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Pro | Met | Asp | Gln |  |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| 20 | Ile | Gln | Ala | Thr | Ile | Ser | Leu | Asn | Thr | Asp | Gln | Thr | Thr | Ala | Ser | Ser |  |
|    | 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |  |
| 25 | Ser | Leu | Pro | Ala | Ala | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Thr | Ser |  |
|    |     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |  |
| 30 | Lys | Pro | Leu | His | Ser | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln |  |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |
| 35 | Ser | Met | Gln | Thr | Val | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Ala | Asn |  |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |
| 40 | Glu | Pro | Glu | Thr | Leu | Lys | Gln | Gln | Ser | Gln | Tyr | Gln | Ala | Thr | Tyr | Asn |  |
|    |     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |
| 45 | Gln | Ser | Phe | Ser | Ser | Gln | Pro | His | Gln | Val | Glu | Gln | Thr | Glu | Leu | Gln |  |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |  |
| 50 | Gln | Asp | Gln | Leu | Gln | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Gln | Asp |  |
|    |     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |  |
| 55 | Gln | Pro | His | Gln | Val | Pro | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn |  |
|    |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |
| 60 | Thr | Gly | Phe | Pro | Arg | Ser | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val |  |
|    |     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |
| 65 | Ser | Arg | Gly | Gly | Ser | Arg | Gly | Ala | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg |  |
|    |     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |
| 70 | Gly | Pro | Ala | Asn | Gly | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser |  |
|    | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |  |
| 75 | Phe | Ser | Asn | Thr | Pro | Asn | Ser | Gly | Tyr | Ser | Gln | Ser | Gln | Phe | Thr | Ala |  |
|    |     |     |     | 645 |     |     |     |     |     | 650 |     |     |     |     | 655 |     |  |

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Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe  
660 665 670

5 Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn  
675 680 685

10 Ile Leu Trp Trp  
690

<210> 29

<211> 2109

<212> DNA

15 <213> Gallus gallus

<220>

<221> CDS

<222> (1) .. (2109)

20 <223>

<400> 29

25

30

35

40

45

50

55

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|    |                                                                 |     |
|----|-----------------------------------------------------------------|-----|
|    | atg ccc tcg gct acc aac ggc acc atg gcg agc agc agc ggg aag gcg | 48  |
|    | Met Pro Ser Ala Thr Asn Gly Thr Met Ala Ser Ser Ser Gly Lys Ala |     |
|    | 1 5 10 15                                                       |     |
| 5  | ggc ccg ggc ggc aac gag cag gcc ccg gcg gcg gca gcg gcg gcc ccg | 96  |
|    | Gly Pro Gly Gly Asn Glu Gln Ala Pro Ala Ala Ala Ala Ala Ala Pro |     |
|    | 20 25 30                                                        |     |
| 10 | cag gcg tcg ggc ggc agc atc acc tcg gtt cag acc gag gcc atg aag | 144 |
|    | Gln Ala Ser Gly Gly Ser Ile Thr Ser Val Gln Thr Glu Ala Met Lys |     |
|    | 35 40 45                                                        |     |
| 15 | cag atc ttg gga gtg atc gac aaa aag ctc cgc aac ctc gag aag aaa | 192 |
|    | Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys |     |
|    | 50 55 60                                                        |     |
| 20 | aag agc aaa ctt gac gat tac cag gaa cga atg aac aag ggg gaa cgt | 240 |
|    | Lys Ser Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg |     |
|    | 65 70 75 80                                                     |     |
| 25 | cta aat caa gat caa ctg gat gca gtg tca aaa tac cag gaa gtg aca | 288 |
|    | Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr |     |
|    | 85 90 95                                                        |     |
| 30 | aat aac ctg gaa ttc gct aaa gaa ctg cag agg agc ttt atg gca ctg | 336 |
|    | Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu |     |
|    | 100 105 110                                                     |     |
| 35 | agc caa gat atc cag aaa aca ata aaa aag acg gct cgc agg gag cag | 384 |
|    | Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln |     |
|    | 115 120 125                                                     |     |
| 40 | ctg atg aga gaa gag gct gag cag aag cgt tta aag act gtg cta gag | 432 |
|    | Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu |     |
|    | 130 135 140                                                     |     |
| 45 | ctg cag ttc att ttg gac aag ttg ggt gac gat gaa gtg cgc agt gac | 480 |
|    | Leu Gln Phe Ile Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Ser Asp |     |
|    | 145 150 155 160                                                 |     |
| 50 | ttg aaa caa gga tca aat gga gta ccg gta ctg aca gag gag gaa ctg | 528 |
| 55 |                                                                 |     |

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |      |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
|    | Leu | Lys | Gln | Gly | Ser | Asn | Gly | Val | Pro | Val | Leu | Thr | Glu | Glu | Glu | Leu |      |
|    |     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |      |
| 5  | aca | atg | ctg | gat | gaa | ttt | tac | aag | cta | gtt | tac | cct | gaa | agg | gac | atg | 576  |
|    | Thr | Met | Leu | Asp | Glu | Phe | Tyr | Lys | Leu | Val | Tyr | Pro | Glu | Arg | Asp | Met |      |
|    |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |      |
| 10 | aac | atg | agg | ttg | aat | gag | cag | tat | gag | caa | gca | tct | gtt | cac | ctg | tgg | 624  |
|    | Asn | Met | Arg | Leu | Asn | Glu | Gln | Tyr | Glu | Gln | Ala | Ser | Val | His | Leu | Trp |      |
|    |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |      |
| 15 | gac | tta | ctg | gaa | ggg | aag | gaa | aaa | ccc | gtt | tgt | gga | aca | acc | tat | aaa | 672  |
|    | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys | Gly | Thr | Thr | Tyr | Lys |      |
|    |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |      |
| 20 | gcc | ctg | aag | gag | gtt | gtt | gaa | cgt | att | ctt | caa | act | agt | tac | ttt | gat | 720  |
|    | Ala | Leu | Lys | Glu | Val | Val | Glu | Arg | Ile | Leu | Gln | Thr | Ser | Tyr | Phe | Asp |      |
|    |     | 225 |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |      |
| 25 | agc | acc | cat | aac | cat | cag | aac | ggg | tta | tgt | gag | gaa | gaa | gag | gca | gca | 768  |
|    | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala |      |
|    |     |     |     |     | 245 |     |     |     | 250 |     |     |     |     |     | 255 |     |      |
| 30 | ccc | aca | cct | gca | gta | gaa | gac | act | gta | gca | gaa | gct | gag | cct | gat | cca | 816  |
|    | Pro | Thr | Pro | Ala | Val | Glu | Asp | Thr | Val | Ala | Glu | Ala | Glu | Pro | Asp | Pro |      |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |      |
| 35 | gca | gaa | gaa | ttt | act | gaa | cct | act | gaa | gtt | gaa | tcg | act | gag | tat | gta | 864  |
|    | Ala | Glu | Glu | Phe | Thr | Glu | Pro | Thr | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val |      |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |      |
| 40 | aac | aga | caa | ttc | atg | gca | gag | act | cag | ttc | agc | agt | agt | gag | aag | gaa | 912  |
|    | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Ser | Glu | Lys | Glu |      |
|    |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |      |
| 45 | cag | gta | gat | gag | tgg | aca | gtt | gaa | acg | gtt | gag | gtt | gta | aat | tca | ctg | 960  |
|    | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu |      |
|    |     | 305 |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |      |
| 50 | cag | caa | caa | aca | caa | gct | aca | tct | cct | cca | gtt | cct | gaa | cct | cat | aca | 1008 |
|    | Gln | Gln | Gln | Thr | Gln | Ala | Thr | Ser | Pro | Pro | Val | Pro | Glu | Pro | His | Thr |      |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |      |
| 55 | ctc | act | act | gtg | gct | caa | gca | gat | cct | ctt | gtt | aga | aga | cag | aga | gta | 1056 |
|    | Leu | Thr | Thr | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val |      |
|    |     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |      |
| 60 | cag | gac | ctt | atg | gcc | cag | atg | cag | ggg | cca | tat | aac | ttc | atg | cag | gac | 1104 |
|    | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Met | Gln | Asp |      |
|    |     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |      |
| 65 | tct | atg | ctg | gag | ttt | gag | aac | cag | aca | ctt | gat | cct | gcc | att | gta | tct | 1152 |
|    | Ser | Met | Leu | Glu | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser |      |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |      |
| 70 | gca | cag | ccc | atg | aat | cca | gca | cag | aat | ttg | gac | atg | ccg | caa | atg | gtc | 1200 |
|    | Ala | Gln | Pro | Met | Asn | Pro | Ala | Gln | Asn | Leu | Asp | Met | Pro | Gln | Met | Val |      |
|    |     | 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |      |
| 75 | tgc | cct | cca | gtt | cat | act | gag | tca | aga | ctt | gcc | cag | cct | aat | caa | gtt | 1248 |
|    | Cys | Pro | Pro | Val | His | Thr | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val |      |
|    |     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |      |
| 80 | cct | gtg | caa | cca | gaa | gct | acg | cag | gtt | ccc | ttg | gtt | tca | tct | aca | agt | 1296 |
|    | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser |      |

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|    | 420                                                                                                                                                   | 425  | 430 |  |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----|--|
| 5  | gag gga tat aca gcc tcc cag ccc atg tat cag cct tct cat acc aca<br>Glu Gly Tyr Thr Ala Ser Gln Pro Met Tyr Gln Pro Ser His Thr Thr<br>435 440 445     | 1344 |     |  |
| 10 | gag caa cgg cca cag aag gaa tcc att gac cag att cag gct tca atg<br>Glu Gln Arg Pro Gln Lys Glu Ser Ile Asp Gln Ile Gln Ala Ser Met<br>450 455 460     | 1392 |     |  |
| 15 | tca ctg aat gca gac cag acc ccg tca tca tca tca ctt ccc act gca<br>Ser Leu Asn Ala Asp Gln Thr Pro Ser Ser Ser Ser Leu Pro Thr Ala<br>465 470 475 480 | 1440 |     |  |
| 20 | tcc cag ccg caa gtt ttc caa gct gga tct agc aaa cct ttg cat agc<br>Ser Gln Pro Gln Val Phe Gln Ala Gly Ser Ser Lys Pro Leu His Ser<br>485 490 495     | 1488 |     |  |
| 25 | agc gga atc aat gtt aat gca gct cca ttc caa tcc atg caa aca gta<br>Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val<br>500 505 510     | 1536 |     |  |
| 30 | ttc aac atg aat gca cct gtt cct cct gtt aat gag cca gaa gcc ctt<br>Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Ala Leu<br>515 520 525     | 1584 |     |  |
| 35 | aag caa caa aat cag tac cag gcc agt tac aac cag agt ttc tcc aat<br>Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Asn<br>530 535 540     | 1632 |     |  |
| 40 | cag cca cac caa gta gaa caa tca gat ctt cag caa gaa cag ctc cag<br>Gln Pro His Gln Val Glu Gln Ser Asp Leu Gln Gln Glu Gln Leu Gln<br>545 550 555 560 | 1680 |     |  |
| 45 | aca gtg gtt ggt act tac cat ggt tct ccg gac cag acc cat caa gtg<br>Thr Val Val Gly Thr Tyr His Gly Ser Pro Asp Gln Thr His Gln Val<br>565 570 575     | 1728 |     |  |
| 50 | gca gga aac cac cag caa cct ccc cag cag aat act gga ttt cca cgc<br>Ala Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg<br>580 585 590     | 1776 |     |  |
| 55 | aac agt cag cct tat tac aac agt cgg gga gtg tct cgt ggt gga tca<br>Asn Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser<br>595 600 605     | 1824 |     |  |
| 60 | cgt ggg act cgt gga ttg atg aat ggt tac agg gga cct gca aat gga<br>Arg Gly Thr Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly<br>610 615 620     | 1872 |     |  |
| 65 | ttt aga gga gga tat gat ggc tac cgt cct tca ttt tcc aac act ccg<br>Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro<br>625 630 635 640 | 1920 |     |  |
| 70 | aac agt ggt tac acg cag ccc caa ttt aat gct cct cga gat tat tca<br>Asn Ser Gly Tyr Thr Gln Pro Gln Phe Asn Ala Pro Arg Asp Tyr Ser<br>645 650 655     | 1968 |     |  |
| 75 | aac tac cag cgg gat gga tat cag cag aac ttc aaa cgt ggt tct gga<br>Asn Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly<br>660 665 670     | 2016 |     |  |
| 80 | caa agt ggg cct ccg gga gct cct cga ggt cgt gga ggg ccc cca aga<br>Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg<br>675 680 685     | 2064 |     |  |

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cca aac aga ggg atg cct caa atg aac gct cag caa gtg aat taa 2109  
 Pro Asn Arg Gly Met Pro Gln Met Asn Ala Gln Gln Val Asn  
 690 695 700

5 <210> 30  
 <211> 702  
 <212> PRT  
 <213> Gallus gallus

10 <400> 30

Met Pro Ser Ala Thr Asn Gly Thr Met Ala Ser Ser Ser Gly Lys Ala  
 1 5 10 15

15 Gly Pro Gly Gly Asn Glu Gln Ala Pro Ala Ala Ala Ala Ala Pro  
 20 25 30

20 Gln Ala Ser Gly Gly Ser Ile Thr Ser Val Gln Thr Glu Ala Met Lys  
 35 40 45

25 Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys  
 50 55 60

Lys Ser Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg  
 65 70 75 80

30 Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr  
 85 90 95

35 Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu  
 100 105 110

40 Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln  
 115 120 125

Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu  
 130 135 140

45 Leu Gln Phe Ile Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Ser Asp  
 145 150 155 160

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

Thr Met Leu Asp Glu Phe Tyr Lys Leu Val Tyr Pro Glu Arg Asp Met  
 180 185 190

55 Asn Met Arg Leu Asn Glu Gln Tyr Glu Gln Ala Ser Val His Leu Trp  
 195 200 205

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Asp | Leu | Leu | Glu | Gly | Lys | Glu | Lys | Pro | Val | Cys | Gly | Thr | Thr | Tyr | Lys |  |
|    | 210 |     |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 5  | Ala | Leu | Lys | Glu | Val | Val | Glu | Arg | Ile | Leu | Gln | Thr | Ser | Tyr | Phe | Asp |  |
|    | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
|    | Ser | Thr | His | Asn | His | Gln | Asn | Gly | Leu | Cys | Glu | Glu | Glu | Glu | Ala | Ala |  |
| 10 |     |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
|    | Pro | Thr | Pro | Ala | Val | Glu | Asp | Thr | Val | Ala | Glu | Ala | Glu | Pro | Asp | Pro |  |
|    |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 15 | Ala | Glu | Glu | Phe | Thr | Glu | Pro | Thr | Glu | Val | Glu | Ser | Thr | Glu | Tyr | Val |  |
|    |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
|    | Asn | Arg | Gln | Phe | Met | Ala | Glu | Thr | Gln | Phe | Ser | Ser | Ser | Glu | Lys | Glu |  |
| 20 |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
|    | Gln | Val | Asp | Glu | Trp | Thr | Val | Glu | Thr | Val | Glu | Val | Val | Asn | Ser | Leu |  |
|    | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| 25 | Gln | Gln | Gln | Thr | Gln | Ala | Thr | Ser | Pro | Pro | Val | Pro | Glu | Pro | His | Thr |  |
|    |     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |
|    | Leu | Thr | Thr | Val | Ala | Gln | Ala | Asp | Pro | Leu | Val | Arg | Arg | Gln | Arg | Val |  |
| 30 |     |     |     | 340 |     |     |     | 345 |     |     |     |     |     | 350 |     |     |  |
|    | Gln | Asp | Leu | Met | Ala | Gln | Met | Gln | Gly | Pro | Tyr | Asn | Phe | Met | Gln | Asp |  |
|    |     | 355 |     |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |  |
| 35 | Ser | Met | Leu | Glu | Phe | Glu | Asn | Gln | Thr | Leu | Asp | Pro | Ala | Ile | Val | Ser |  |
|    |     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
|    | Ala | Gln | Pro | Met | Asn | Pro | Ala | Gln | Asn | Leu | Asp | Met | Pro | Gln | Met | Val |  |
| 40 |     | 385 |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |  |
|    | Cys | Pro | Pro | Val | His | Thr | Glu | Ser | Arg | Leu | Ala | Gln | Pro | Asn | Gln | Val |  |
|    |     |     |     | 405 |     |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| 45 | Pro | Val | Gln | Pro | Glu | Ala | Thr | Gln | Val | Pro | Leu | Val | Ser | Ser | Thr | Ser |  |
|    |     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |
|    | Glu | Gly | Tyr | Thr | Ala | Ser | Gln | Pro | Met | Tyr | Gln | Pro | Ser | His | Thr | Thr |  |
| 50 |     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |  |
|    | Glu | Gln | Arg | Pro | Gln | Lys | Glu | Ser | Ile | Asp | Gln | Ile | Gln | Ala | Ser | Met |  |
|    |     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |  |
| 55 | Ser | Leu | Asn | Ala | Asp | Gln | Thr | Pro | Ser | Ser | Ser | Ser | Leu | Pro | Thr | Ala |  |

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|    | 465 |     | 470 |     | 475 |     | 480 |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 5  | Ser | Gln | Pro | Gln | Val | Phe | Gln | Ala | Gly | Ser | Ser | Lys | Pro | Leu | His | Ser |
|    |     |     |     | 485 |     |     |     |     |     | 490 |     |     |     |     | 495 |     |
| 10 | Ser | Gly | Ile | Asn | Val | Asn | Ala | Ala | Pro | Phe | Gln | Ser | Met | Gln | Thr | Val |
|    |     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| 15 | Phe | Asn | Met | Asn | Ala | Pro | Val | Pro | Pro | Val | Asn | Glu | Pro | Glu | Ala | Leu |
|    |     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| 20 | Lys | Gln | Gln | Asn | Gln | Tyr | Gln | Ala | Ser | Tyr | Asn | Gln | Ser | Phe | Ser | Asn |
|    |     | 530 |     |     |     |     | 535 |     |     |     | 540 |     |     |     |     |     |
| 25 | Gln | Pro | His | Gln | Val | Glu | Gln | Ser | Asp | Leu | Gln | Gln | Glu | Gln | Leu | Gln |
|    | 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     | 560 |     |
| 30 | Thr | Val | Val | Gly | Thr | Tyr | His | Gly | Ser | Pro | Asp | Gln | Thr | His | Gln | Val |
|    |     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |
| 35 | Ala | Gly | Asn | His | Gln | Gln | Pro | Pro | Gln | Gln | Asn | Thr | Gly | Phe | Pro | Arg |
|    |     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| 40 | Asn | Ser | Gln | Pro | Tyr | Tyr | Asn | Ser | Arg | Gly | Val | Ser | Arg | Gly | Gly | Ser |
|    |     |     | 595 |     |     |     | 600 |     |     |     |     |     | 605 |     |     |     |
| 45 | Arg | Gly | Thr | Arg | Gly | Leu | Met | Asn | Gly | Tyr | Arg | Gly | Pro | Ala | Asn | Gly |
|    | 610 |     |     |     |     | 615 |     |     |     |     |     | 620 |     |     |     |     |
| 50 | Phe | Arg | Gly | Gly | Tyr | Asp | Gly | Tyr | Arg | Pro | Ser | Phe | Ser | Asn | Thr | Pro |
|    | 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     | 640 |     |
| 55 | Asn | Ser | Gly | Tyr | Thr | Gln | Pro | Gln | Phe | Asn | Ala | Pro | Arg | Asp | Tyr | Ser |
|    |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |     |
| 60 | Asn | Tyr | Gln | Arg | Asp | Gly | Tyr | Gln | Gln | Asn | Phe | Lys | Arg | Gly | Ser | Gly |
|    |     |     | 660 |     |     |     |     | 665 |     |     |     |     |     | 670 |     |     |
| 65 | Gln | Ser | Gly | Pro | Arg | Gly | Ala | Pro | Arg | Gly | Arg | Gly | Gly | Pro | Pro | Arg |
|    |     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| 70 | Pro | Asn | Arg | Gly | Met | Pro | Gln | Met | Asn | Ala | Gln | Gln | Val | Asn |     |     |
|    |     | 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |

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 aattaaccct cactaaaggg 20  
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 1 5  
 <210> 38  
 <211> 17  
 <212> PRT

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<213> Gallus gallus

<400> 38

5           Ala Ile Asn Lys Phe Gly Asn Ser Thr Gly His Gly Ala Ala Val Lys  
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10           Gly

<210> 39

<211> 19

<212> PRT

<213> Gallus gallus

15

<400> 39

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          1                   5                   10                   15

20

Ile Asp Ala

<210> 40

25

<211> 128

<212> PRT

<213> Gallus gallus

<400> 40

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35

40

45

50

55

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|    |                                                                                                                     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|---------------------------------------------------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Ala                                                                                                                 | Val | Thr | Leu | Asp | Glu | Ser | Gly | Gly | Gly | Leu | Gln | Met | Ser | Arg | Gly |  |
|    | 1                                                                                                                   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 5  | Gly                                                                                                                 | Leu | Ser | Leu | Val | Cys | Lys | Ala | Ser | Gly | Phe | Asp | Phe | Ser | Ser | Tyr |  |
|    |                                                                                                                     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Gln                                                                                                                 | Met | Asn | Trp | Ile | Arg | Gln | Ala | Pro | Gly | Lys | Gly | Leu | Glu | Phe | Val |  |
|    |                                                                                                                     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 15 | Ala                                                                                                                 | Ala | Ile | Asn | Lys | Phe | Gly | Asn | Ser | Thr | Gly | His | Gly | Ala | Ala | Val |  |
|    |                                                                                                                     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Lys                                                                                                                 | Gly | Arg | Val | Thr | Ile | Ser | Arg | Asp | Asn | Gly | Gln | Ser | Thr | Val | Arg |  |
|    | 65                                                                                                                  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 25 | Leu                                                                                                                 | Gln | Leu | Asn | Asn | Leu | Arg | Ala | Glu | Asp | Thr | Ala | Ile | Tyr | Phe | Cys |  |
|    |                                                                                                                     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 30 | Thr                                                                                                                 | Lys | His | Ala | Tyr | Gly | Tyr | Cys | Gly | Ser | Gly | Thr | Trp | Cys | Ala | Ala |  |
|    |                                                                                                                     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 35 | Gly                                                                                                                 | Glu | Ile | Asp | Ala | Trp | Gly | His | Gly | Thr | Glu | Val | Ile | Val | Ser | Ser |  |
|    |                                                                                                                     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| 40 | <div>&lt;210&gt; 41</div> <div>&lt;211&gt; 9</div> <div>&lt;212&gt; PRT</div> <div>&lt;213&gt; Gallus gallus</div>  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 | <div>&lt;400&gt; 41</div>                                                                                           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 50 | <div>Ser Gly Gly Gly Ser Tyr Ser Tyr Gly</div> <div>1 5</div>                                                       |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 55 | <div>&lt;210&gt; 42</div> <div>&lt;211&gt; 7</div> <div>&lt;212&gt; PRT</div> <div>&lt;213&gt; Gallus gallus</div>  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <div>&lt;400&gt; 42</div>                                                                                           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <div>Asn Asn Lys Arg Pro Ser Asp</div> <div>1 5</div>                                                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <div>&lt;210&gt; 43</div> <div>&lt;211&gt; 10</div> <div>&lt;212&gt; PRT</div> <div>&lt;213&gt; Gallus gallus</div> |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <div>&lt;400&gt; 43</div>                                                                                           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |

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Ser Gly Asp Ser Thr Asp Thr Ala Val Phe  
1 5 10

<210> 44  
<211> 108  
<212> PRT  
<213> Gallus gallus

<400> 44

Gln Ala Ala Ser Thr Gln Pro Ser Ser Val Ser Ala Asn Pro Gly Glu  
1 5 10 15

Thr Val Glu Ile Thr Cys Ser Gly Gly Gly Ser Tyr Ser Tyr Gly Trp  
20 25 30

Phe Gln Gln Lys Ser Pro Gly Ser Ala Pro Val Thr Val Ile Tyr Tyr  
35 40 45

Asn Asn Lys Arg Pro Ser Asp Ile Pro Ser Arg Phe Ser Gly Ser Lys  
50 55 60

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

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

Phe Gly Ala Gly Thr Thr Leu Thr Val Leu Gly Gln  
100 105

<210> 45  
<211> 384  
<212> DNA  
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<400> 45

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gtctgcaagg cctccgggtt cgacttcagc agctatcaga tgaactggat ccgacaggca 120  
cccggaag ggctgggagt cgctcgtgct attaacaaat ttgggaatag tacgggtcat 180  
ggggcggcag tgaagggccg tgtcaccatc tcgagggaca acgggcagag cacagtgagg 240  
ctgcagctga acaacctcag ggctgaggac accgccatct acttctgcac aaaacatgcc 300  
tacggttatt gtggtagtgg tacttgggtg gctgctggtg agatcgacgc atggggccac 360  
gggaccgaag tcatcgtctc ctcc 384

<210> 46

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<211> 324  
 <212> DNA  
 <213> Gallus gallus

5 <400> 46

|    |                                                                    |     |
|----|--------------------------------------------------------------------|-----|
|    | caggcagcta gcactcagcc gtcctcgggtg tcagcgaacc cgggagagac cgtcgagatc | 60  |
| 10 | acctgctccg ggggtggcag ctatagctat ggctgggttcc agcagaagtc tcctggcagt | 120 |
|    | gcccctgtca ctgtgatcta ttacaacaac aagagaccct cggacatccc ttcacgattc  | 180 |
|    | tccggttcca aatccggctc cacgggcaca ttaaccatca ctgggggtcca agccgacgac | 240 |
| 15 | gaggctgtct attactgtgg gagtggagac agcactgata ctgctgtatt gggggccggg  | 300 |
|    | acaaccctga ccgtcctagg ccag                                         | 324 |

20 <210> 47  
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 <213> Gallus gallus

25 <400> 47

Phe Asp Met Gly  
 1

30 <210> 48  
 <211> 17  
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 <213> Gallus gallus

35 <400> 48

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Ile | Asn | Asp | Ala | Gly | Ser | Arg | Thr | Trp | Tyr | Ala | Thr | Ala | Val | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

40 Gly

45 <210> 49  
 <211> 12  
 <212> PRT  
 <213> Gallus gallus

<400> 49

|     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Gly | Tyr | Val | Gly | Ala | Gly | Ala | Ile | Asp | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |

55 <210> 50  
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 <213> Gallus gallus

<400> 50

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

  

|    |     |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Ser | Gly | Gly | Ser | Gly | Tyr | Tyr | Gly |  |
|    | 1   |     |     |     | 5   |     |     |     |  |
| 40 |     |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |  |
| 45 |     |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |  |
| 50 |     |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |  |
| 55 |     |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |     |  |

  

|    |     |     |     |     |     |     |     |  |
|----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Asn | Asp | Lys | Arg | Pro | Ser | Asp |  |
|    | 1   |     |     |     | 5   |     |     |  |
| 50 |     |     |     |     |     |     |     |  |
|    |     |     |     |     |     |     |     |  |
| 55 |     |     |     |     |     |     |     |  |
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 <212> PRT  
 <213> Gallus gallus

<400> 52

<210> 53  
 <211> 10  
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 <213> Gallus gallus

<400> 53

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Arg Tyr Asp Ser Thr Asp Ser Gly Ile Phe  
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<210> 54  
<211> 105  
<212> PRT  
<213> Gallus gallus

<400> 54

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Val Lys Ile Thr Cys Ser Gly Gly Ser Gly Tyr Tyr Gly Trp Tyr Gln  
20 25 30

Gln Gln Lys Ser Pro Gly Ser Ala Pro Val Thr Val Ile Tyr Gln Asn  
35 40 45

Asp Lys Arg Pro Ser Asp Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser  
50 55 60

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

Ala Val Tyr Phe Cys Gly Arg Tyr Asp Ser Thr Asp Ser Gly Ile Phe  
85 90 95

Gly Ala Gly Thr Thr Leu Thr Val Leu  
100 105

<210> 55  
<211> 363  
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<213> Gallus gallus

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gcgcctggca aggggctgga attcgtcgct caaattaatg atgctggtag taggacatgg 180  
tacgacgacag cgggtgaagg cctgtgccacc atctcgaggg acaacgggca gaccacagtg 240  
aggctgcagc tgaacaacct cagggctgag gacaccggca cctactactg caccagaggt 300  
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tcg 363

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cctgtcactg tgatctatca aaacgacaag agaccctcgg acatcccttc acgattctcc      180
ggttctggat caggctccac aaacacatta accatcactg gggccaagc cgaggacgag      240
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20

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<400> 57

Gly Tyr Asp Met Leu  
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<210> 58  
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<400> 58

Gly Ile Gly Ser Thr Gly Gly Gly Thr Asp Tyr Gly Ala Ala Val Lys  
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Gly

<210> 59  
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<400> 59

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Val Ala Gly Gly Cys Asn Ser Gly Tyr Cys Arg Asp Ser Pro Gly Ser  
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Ile Asp Ala

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<213> Gallus gallus

<400> 60

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Ala Leu Ser Leu Val Cys Lys Ala Ser Gly Phe Thr Phe Ser Gly Tyr  
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15  
Asp Met Leu Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

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

20  
Lys Gly Arg Ala Thr Ile Ser Arg Asp Asn Gly Gln Ser Thr Val Arg  
65 70 75 80

25  
Leu Gln Leu Asn Asn Leu Arg Ala Glu Asp Thr Ala Thr Tyr Tyr Cys  
85 90 95

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

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Gly Ser Ile Asp Ala Trp Gly His Gly Thr Glu Val Ile Val Ser  
115 120 125

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Ser Gly Gly Gly Ser Arg Asn Tyr Tyr Gly  
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Asp Asp Gln Arg Pro Ser Asn  
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<400> 63

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<400> 64

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Val Lys Ile Thr Cys Ser Gly Gly Gly Ser Arg Asn Tyr Tyr Gly Trp  
20 25 30

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Tyr Gln Gln Lys Ser Pro Gly Ser Val Pro Val Thr Val Ile Tyr Tyr  
35 40 45

25

Asp Asp Gln Arg Pro Ser Asn Ile Pro Ser Arg Phe Ser Gly Ala Leu  
50 55 60

30

Ser Gly Ser Thr Ser Thr Leu Thr Ile Thr Gly Val Gln Ala Asp Asp  
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Glu Ala Val Tyr Phe Cys Gly Ser Ala Asp Ser Asn Thr Tyr Glu Gly  
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<213> Gallus gallus

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&lt;210&gt; 66

&lt;211&gt; 321

&lt;212&gt; DNA

&lt;213&gt; Gallus gallus

&lt;400&gt; 66

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&lt;210&gt; 67

&lt;211&gt; 5

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 67

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|-----|-----|-----|-----|-----|
| Asp | Tyr | Asn | Met | Asp |
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&lt;210&gt; 68

&lt;211&gt; 17

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 68

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ile | Asn | Pro | Asn | Tyr | Asp | Ser | Thr | Ser | Tyr | Asn | Gln | Lys | Phe | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Gly

&lt;210&gt; 69

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;400&gt; 69

|     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Ser | Tyr | Asp | Tyr | Glu | Gly | Phe | Ala | Tyr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |

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&lt;211&gt; 148

&lt;212&gt; PRT

# EP 2 740 489 B1

<213> Mus musculus

<400> 70

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      20          25          30

15     Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
      35          40          45

20     Thr Asp Tyr Asn Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu
      50          55          60

25     Glu Trp Ile Gly Asp Ile Asn Pro Asn Tyr Asp Ser Thr Ser Tyr Asn
      65          70          75          80

30     Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
      85          90          95

35     Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Thr Ala Val
      100         105         110

40     Tyr Tyr Cys Ala Arg Ser Arg Ser Tyr Asp Tyr Glu Gly Phe Ala Tyr
      115         120         125

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

50     Pro Ser Val Tyr
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<211> 11

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<213> Mus musculus

<400> 71

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      1          5          10

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<211> 6

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<213> Mus musculus

<400> 72

# EP 2 740 489 B1

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10 <400> 73

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<213> Mus musculus  
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Gln Asn Leu Leu Ser Ile Val Asn Arg Tyr His Tyr Met Ser Gly Asn  
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30 Pro Pro Lys Leu Leu Val Tyr Pro Ala Leu Leu Ile Tyr Glu Ala Ser  
35 40 45

35 Ile Thr Lys Ser Cys Val Pro Asp Arg Phe Thr Arg Ser Gly Ser Gly  
50 55 60

40 Thr Asn Phe Thr Leu Thr Ile Asn Phe Val His Ala Asp Asp Leu Ile  
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Phe Tyr Tyr Cys Gln His Asn Arg Gly Ser Phe Leu Pro Ser Ser Ser  
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100 105

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<212> PRT

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<400> 77

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<210> 78

<211> 17

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Gly

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Phe Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly  
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Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr  
 35 40 45

30

Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg  
 50 55 60

35

Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala  
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Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Ala Asn Trp Ala Phe Asp  
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<400> 82

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5

<210> 83

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Tyr Ala Ser Gln Ser Ile Ser  
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Ser Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser  
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Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu  
20 25 30

30

Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe  
35 40 45

35

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val  
50 55 60

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Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp  
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Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gln  
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EP 2 740 489 B1

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

Gly Gly Thr Asn Tyr Asn Glu Lys Phe Lys Gly Lys Ala Ile Leu Thr  
50 55 60

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr  
65 70 75 80

Ser Asp Glu Phe Ala Val Tyr Phe Cys Ala Arg Glu Lys Ile Tyr Asp  
85 90 95

Asp Tyr Tyr Glu Gly Tyr Phe Asp Val Trp Gly Ala Gly Pro Arg His  
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Leu Leu Ala Ser Leu Ser  
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His Tyr Ser Lys Leu Pro Leu Thr Phe  
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25

Ile Gly Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val  
 35 40 45

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Lys Leu Leu Ile Tyr Tyr Thr Ser Asn Leu His Ser Gly Val Pro Ser  
 50 55 60

35

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

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Gly

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                                    20                    25                    30

20                   Thr Pro Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Pro Gly Asn  
                                    35                    40                    45

25                   Gly Gly Thr Asn Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr  
                                    50                    55                    60

30                   Ala Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Ile Ser Ser Leu Thr  
                                    65                    70                    75                    80

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

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EP 2 740 489 B1

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30 Cys Arg Ala Ser Gly Asn Ile His Asn Tyr Leu Thr Trp Tyr Gln Gln  
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Lys Gln Gly Lys Ser Pro Gln Leu Leu Val Tyr Asn Ala Lys Thr Leu  
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35 Ala Asp Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln  
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40 Tyr Ser Leu Lys Ile Asn Arg Leu Gln Pro Glu Asp Phe Gly Ser Tyr  
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<400> 107

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Gly

<210> 109  
 <211> 12  
 <212> PRT  
 <213> Mus musculus

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<400> 109

5                   Ser Leu Gly Arg Gly Gly Pro Tyr Tyr Phe Asp Tyr  
                  1                   5                   10

<210> 110  
<211> 114  
<212> PRT  
<213> Mus musculus

10

<400> 110

15           Asp Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys  
          1                   5                   10                   15

          Ala Ser Gly Tyr Thr Phe Thr Asp His Ser Ile His Trp Val Gln Gln  
                  20                   25                   30

20           Lys Pro Glu Gln Gly Leu Glu Trp Ile Gly Tyr Ile Ser Pro Gly Asn  
                  35                   40                   45

25           Gly Asn Ile Lys Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr  
                  50                   55                   60

30           Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Asn Ser Leu Thr  
          65                   70                   75                   80

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

35           Gly Pro Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val  
                  100                   105                   110

40           Ser Ser

<210> 111  
<211> 16  
<212> PRT  
<213> Mus musculus

45

<400> 111

50           Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr  
          1                   5                   10                   15

<210> 112  
<211> 7  
<212> PRT  
<213> Mus musculus

55

<400> 112

# EP 2 740 489 B1

Arg Met Ser Asn Leu Ala Ser  
1 5

<210> 113  
<211> 9  
<212> PRT  
<213> Mus musculus

<400> 113

Met Gln His Arg Glu Tyr Pro Val Thr  
1 5

<210> 114  
<211> 108  
<212> PRT  
<213> Mus musculus

<400> 114

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

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser  
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser  
35 40 45

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

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

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His  
85 90 95

Arg Glu Tyr Pro Val Thr Phe Gly Ser Gly Pro Asn  
100 105

<210> 115  
<211> 342  
<212> DNA  
<213> Mus musculus

<400> 115

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accttcactg accattctat tcactgggtg cagcagaagc ctgaacaggg cctggaatgg 120

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attggatata tttctcccgg aaatggtaat attaagtaca atgagaaatt caagggcaag 180  
gccacactga ctgcagacaa atcctccagc actgcctaca tgcagctcaa cagcctgaca 240  
5 tctgaggatt ctgcagtgtg tttctgtaaa agatctctgg gacgtggggg cccgtactac 300  
tttgactact ggggcccaagg gaccacgggc accgtctcct ca 342

10 <210> 116  
<211> 323  
<212> DNA  
<213> Mus musculus

15 <400> 116

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20 tcctgcagag gccaggccag tctcctcagc tcctgatata tcggatgtcc aaccttgcct 180  
caggagtccc agacagggtc agtggcagtg ggtcaggaac tgctttcaca ctgagaatca 240  
gtagagtgga ggctgaggat gtgggtgttt attactgtat gcaacatcga gaatatccgg 300  
25 tcacgttcgg ttctggacca aac 323

30 <210> 117  
<211> 5  
<212> PRT  
<213> Mus musculus

<400> 117

35 Ser Tyr Trp Ile Glu  
1 5

40 <210> 118  
<211> 17  
<212> PRT  
<213> Mus musculus

<400> 118

45 Glu Ile Leu Pro Gly Ser Gly Ser Thr Asn Tyr Asn Glu Lys Phe Lys  
1 5 10 15

50 Gly

<210> 119  
<211> 11  
<212> PRT  
<213> Mus musculus

55 <400> 119

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Tyr Tyr Trp Tyr Phe Asp Val Trp Ala Gln Asp  
1 5 10

<210> 120  
<211> 111  
<212> PRT  
<213> Mus musculus

<400> 120

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

Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr  
20 25 30

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

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Asn Tyr Asn Glu Lys Phe  
50 55 60

Lys Gly Lys Ala Thr Phe Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr  
65 70 75 80

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

Ala Ser Tyr Tyr Trp Tyr Phe Asp Val Trp Ala Gln Asp His Val  
100 105 110

<210> 121  
<211> 15  
<212> PRT  
<213> Mus musculus

<400> 121

Ser Ser Lys Asn Leu Leu His Ser Asn Gly Ile Thr Tyr Leu Tyr  
1 5 10 15

<210> 122  
<211> 7  
<212> PRT  
<213> Mus musculus

<400> 122

Arg Val Ser Asn Leu Ala Ser  
1 5

<210> 123  
<211> 9

EP 2 740 489 B1

<212> PRT  
<213> Mus musculus

<400> 123

5

Ala Gln Leu Leu Glu Leu Pro Tyr Thr  
1 5

<210> 124  
<211> 109  
<212> PRT  
<213> Mus musculus

10

<400> 124

15

Ile Val Met Thr Gln Ala Ala Phe Ser Asn Pro Val Thr Leu Gly Thr  
1 5 10 15

20

Ser Ala Ser Ile Ser Cys Arg Ser Ser Lys Asn Leu Leu His Ser Asn  
20 25 30

25

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

30

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

Arg Phe Ser Gly Ser Glu Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser  
65 70 75 80

35

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

40

Glu Leu Pro Tyr Thr Ser Glu Gly Thr Lys Arg Trp Glu  
100 105

<210> 125  
<211> 333  
<212> DNA  
<213> Mus musculus

45

<400> 125

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55

# EP 2 740 489 B1

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 cctggacatg gccttgagtg gattggagag attttacctg gaagtggtag tactaactac 180  
 aatgagaagt tcaagggcaa ggccacattc actgcagata catcctccaa cacagcctac 240  
 10 atgcaactca gcagcctgac atctgaggac tctgccgtct attactgtgc aagttactac 300  
 tgggtacttcg atgtctgggc gcaggaccac gta 333

<210> 126  
 <211> 327  
 15 <212> DNA  
 <213> Mus musculus

<400> 126

20 attgtgatga cgcaggctgc cttctccaat ccagtcactc ttggaacatc agcttccatc 60  
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 25 ctgcagaggc caggccagtc tcctcagctc ctgatataatc ggggtgtccaa tctggcctca 180  
 ggagtcccaa acaggttcag tggcagtgag tcaggaactg atttcacact gagaatcagc 240  
 agagtggagg ctgaggatgt ggggtgtttat tactgtgctc aactgctaga actcccgtac 300  
 30 acgtcggagg ggaccaagcg ctggggag 327

<210> 127  
 <211> 5  
 35 <212> PRT  
 <213> Mus musculus

<400> 127

40 Ser Phe Gly Met His  
 1 5

<210> 128  
 <211> 17  
 45 <212> PRT  
 <213> Mus musculus

<400> 128

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

Gly

55 <210> 129  
 <211> 11  
 <212> PRT

# EP 2 740 489 B1

<213> Mus musculus

<400> 129

5                   Ile Gly Thr Thr Thr Gly Pro Arg His His Phe  
                  1                   5                   10

<210> 130

<211> 113

10 <212> PRT

<213> Mus musculus

<400> 130

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

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

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

30           Ala Tyr Ile Ser Ser Gly Ser Ser Thr Ile Tyr Tyr Ala Asp Thr Val  
                  50                   55                   60

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

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

40           Ala Ser Thr Ile Gly Thr Thr Thr Gly Pro Arg His His Phe Thr Leu  
                  100                   105                   110

Arg

45 <210> 131

<211> 339

<212> DNA

<213> Mus musculus

50 <400> 131

55

# EP 2 740 489 B1

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 tcctgtgcag cctctggatt cactttcagt agctttggaa tgcactgggt tcgtcaggct 120  
 5 ccagagaagg ggctggagtg ggtcgcatac attagtagtg gcagtagtac catctactat 180  
 gcagacacag tgaagggccg attcaccatc tccagagaca atcccaagaa caccctgttc 240  
 ctgcaaataa ccagtctaag gtctgaggac acggccatgt attactgtgc aagtactata 300  
 10 ggtacgacta ctgggccaag gcaccacttc acgctccgc 339

<210> 132  
 <211> 5  
 15 <212> PRT  
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<400> 132  
 20 Ser Tyr Asp Met Ser  
 1 5

<210> 133  
 <211> 17  
 25 <212> PRT  
 <213> Mus musculus

<400> 133  
 30 Tyr Ile Ser Ser Gly Ala Gly Ser Thr Tyr Tyr Pro Asp Thr Val Lys  
 1 5 10 15

Gly  
 35 <210> 134  
 <211> 11  
 <212> PRT  
 <213> Mus musculus

<400> 134  
 40  
 His Phe Tyr Arg Phe Asp Tyr Trp Gly Gln Gly  
 1 5 10

45 <210> 135  
 <211> 109  
 <212> PRT  
 <213> Mus musculus

50 <400> 135

55

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Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala  
 1 5 10 15  
 5 Ala Ser Gly Phe Ala Phe Ser Ser Tyr Asp Met Ser Trp Ile Arg Gln  
 20 25 30  
 10 Thr Pro Glu Lys Arg Leu Glu Trp Val Ala Tyr Ile Ser Ser Gly Ala  
 35 40 45  
 Gly Ser Thr Tyr Tyr Pro Asp Thr Val Lys Gly Arg Phe Thr Val Ser  
 50 55 60  
 15 Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys  
 65 70 75 80  
 20 Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Phe Tyr Arg Phe  
 85 90 95  
 Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
 100 105  
 25  
 <210> 136  
 <211> 15  
 <212> PRT  
 30 <213> Mus musculus  
 <400> 136  
 Ser Ala Gly Asp Arg Ile Thr Ile Thr Cys Lys Ala Ser Gln Ser  
 1 5 10 15  
 35  
 <210> 137  
 <211> 7  
 <212> PRT  
 40 <213> Mus musculus  
 <400> 137  
 Tyr Ala Ser Asn Arg Tyr Thr  
 1 5  
 45  
 <210> 138  
 <211> 9  
 <212> PRT  
 50 <213> Mus musculus  
 <400> 138  
 Gln Gln Asp Asp Arg Phe Pro Leu Thr  
 1 5  
 55  
 <210> 139  
 <211> 113

# EP 2 740 489 B1

<212> PRT

<213> Mus musculus

<400> 139

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

10

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

15

Cys Lys Ala Ser Gln Ser Val Ser Asn Asp Val Ala Trp Tyr Gln Gln  
35 40 45

20

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

Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Tyr Gly Thr Asp  
65 70 75 80

25

Phe Thr Phe Thr Ile Ser Thr Val Gln Ala Glu Asp Leu Ala Val Tyr  
85 90 95

30

Phe Cys Gln Gln Asp Asp Arg Phe Pro Leu Thr Phe Gly Ala Gly Pro  
100 105 110

Ser

35

<210> 140

<211> 327

<212> DNA

<213> Mus musculus

40

<400> 140

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gctttcagta gctatgacat gtcttggatt cgccagactc cggagaagag gctggaatgg 120

gtcgcataca ttagcagtgg tgctggtagc acctactatc cagacactgt gaaaggccga 180

50

ttcaccgtct ccagagacaa tgccaagaac accctgtatc tgcaaagtag cagtctgaag 240

tctgaggaca cagccatgta ttactgtgca agacatttct accgctttga ctactggggc 300

caagggacca cggtcaccgt ctctca 327

55

<210> 141

<211> 339

<212> DNA

<213> Mus musculus

# EP 2 740 489 B1

<400> 141

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5  ctgcttgat cagcaggaga caggattacc atcacctgca aggccagtca gagtgtgagt      120
aatgatgtag cttggtacca acagaagcca gggcagtctc ctaaactact gatatactat      180
10 gcatccaatc gctacactgg agtccctgat cgcttcactg gcagtggata tgggacggat      240
ttcactttca ccatcagcac tgtgcaggct gaagacctgg cagtttattt ctgtcagcag      300
gatgataggt ttcctctcac gttcgggtgct ggaccaagc      339

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15 <210> 142  
 <211> 5  
 <212> PRT  
 <213> Mus musculus

20 <400> 142

Asn Tyr Gly Met Asn  
 1 5

25 <210> 143  
 <211> 17  
 <212> PRT  
 <213> Mus musculus

30 <400> 143

Trp Ile Asn Thr Tyr Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys  
 1 5 10 15

35 Gly

<210> 144  
 <211> 11  
 40 <212> PRT  
 <213> Mus musculus

<400> 144

45 Gly Ala Trp Phe Ala Tyr Trp Ala Lys Asp Ser  
 1 5 10

<210> 145  
 <211> 112  
 50 <212> PRT  
 <213> Mus musculus

<400> 145

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|    |                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Gln                | Ile | Gln | Leu | Val | Gln | Ser | Gly | Pro | Glu | Leu | Lys | Lys | Pro | Gly | Glu |
|    | 1                  |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| 5  | Thr                | Val | Lys | Ile | Ser | Cys | Lys | Ala | Ser | Gly | Tyr | Thr | Phe | Thr | Asn | Tyr |
|    |                    |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| 10 | Gly                | Met | Asn | Trp | Val | Lys | Gln | Ala | Pro | Gly | Lys | Gly | Leu | Lys | Trp | Met |
|    |                    |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| 15 | Gly                | Trp | Ile | Asn | Thr | Tyr | Thr | Gly | Glu | Pro | Thr | Tyr | Ala | Asp | Asp | Phe |
|    | 50                 |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| 20 | Lys                | Gly | Arg | Phe | Ala | Phe | Ser | Leu | Glu | Thr | Ser | Ala | Ser | Thr | Ala | Tyr |
|    | 65                 |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| 25 | Leu                | Gln | Ile | Asn | Asn | Leu | Lys | Asn | Glu | Asp | Thr | Ala | Thr | Tyr | Phe | Cys |
|    |                    |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| 30 | Ala                | Thr | Gly | Ala | Trp | Phe | Ala | Tyr | Trp | Ala | Lys | Asp | Ser | Ser | Arg | His |
|    |                    |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
|    | <210> 146          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 15           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 146          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 35 | Ser                | Ile | Thr | Cys | Lys | Ala | Ser | Gln | Asp | Val | Gly | Thr | Ala | Val | Ala |     |
|    | 1                  |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| 40 | <210> 147          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 7            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 147          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 45 |                    |     |     |     |     | Trp | Ala | Ser | Thr | Arg | His | Thr |     |     |     |     |
|    |                    |     |     |     |     | 1   |     |     |     | 5   |     |     |     |     |     |     |
| 50 | <210> 148          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 9            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 148          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 55 |                    |     |     |     |     | Gln | Gln | Tyr | Ser | Ser | Tyr | Pro | Leu | Thr |     |     |
|    |                    |     |     |     |     | 1   |     |     |     | 5   |     |     |     |     |     |     |
|    | <210> 149          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 107          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

# EP 2 740 489 B1

<212> PRT

<213> Mus musculus

<400> 149

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Gly Val Glu Gly Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser  
1 5 10 15

10

Thr Ser Val Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp  
20 25 30

15

Val Gly Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro  
35 40 45

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

20

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

25

Asn Val Gln Ser Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Ser  
85 90 95

30

Ser Tyr Pro Leu Thr Phe Gly Ala Gly Pro Ser  
100 105

<210> 150

<211> 336

<212> DNA

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<213> Mus musculus

<400> 150

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ccaggaaaagg gtttaaagtg gatgggctgg ataaacacct acactggaga gccaacatat 180

45

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

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tggtttgctt actgggcca aa ggactcttca cgccac 336

50

<210> 151

<211> 333

<212> DNA

<213> Mus musculus

55

<400> 151

# EP 2 740 489 B1

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cagcagaagt caggcacctc ccccaaaaga tggatttatg acacatccaa actggcttct 180

ggagtccctg ctcgcttcag tggcagtggt tctgggacct cttactctct cacaatcagc 240

10 agcatggagg ctgaagatgc tgccacttat tactgccagc agtggagtag taaccacccc 300

atctcacgtt cgggtgctgga ccaagcgagc tgc 333

15 <210> 152  
<211> 15  
<212> PRT  
<213> Mus musculus

20 <400> 152

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Thr | Met | Thr | Cys | Ser | Ala | Ser | Ser | Ser | Val | Ser | Tyr | Met | His |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |

25 <210> 153  
<211> 7  
<212> PRT  
<213> Mus musculus

30 <400> 153

|     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|
| Asp | Thr | Ser | Lys | Leu | Ala | Ser |
| 1   |     |     |     | 5   |     |     |

35 <210> 154  
<211> 9  
<212> PRT  
<213> Mus musculus

40 <400> 154

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Gln | Trp | Ser | Ser | Asn | Pro | Pro | Ile |
| 1   |     |     |     | 5   |     |     |     |     |

45 <210> 155  
<211> 111  
<212> PRT  
<213> Mus musculus

50 <400> 155

55

# EP 2 740 489 B1

|    |             |              |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-------------|--------------|------------|------------|------------|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Ile         | Ile          | Ser        | Arg        | Gly        | Gln         | Ile | Val | Leu | Thr | Gln | Ser | Pro | Ala | Ile | Met |     |  |
|    | 1           |              |            |            | 5          |             |     |     |     | 10  |     |     |     |     | 15  |     |     |  |
| 5  |             | Ser          | Ala        | Ser        | Pro        | Gly         | Glu | Lys | Val | Thr | Met | Thr | Cys | Ser | Ala | Ser | Ser |  |
|    |             |              |            | 20         |            |             |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Ser         | Val          | Ser        | Tyr        | Met        | His         | Trp | Tyr | Gln | Gln | Lys | Ser | Gly | Thr | Ser | Pro |     |  |
|    |             |              | 35         |            |            |             |     | 40  |     |     |     |     | 45  |     |     |     |     |  |
|    | Lys         | Arg          | Trp        | Ile        | Tyr        | Asp         | Thr | Ser | Lys | Leu | Ala | Ser | Gly | Val | Pro | Ala |     |  |
| 15 |             |              |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    |             |              | 50         |            |            |             |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Arg         | Phe          | Ser        | Gly        | Ser        | Gly         | Ser | Gly | Thr | Ser | Tyr | Ser | Leu | Thr | Ile | Ser |     |  |
|    | 65          |              |            |            |            | 70          |     |     |     |     | 75  |     |     |     |     | 80  |     |  |
|    | Ser         | Met          | Glu        | Ala        | Glu        | Asp         | Ala | Ala | Thr | Tyr | Tyr | Cys | Gln | Gln | Trp | Ser |     |  |
|    |             |              |            |            | 85         |             |     |     |     | 90  |     |     |     |     | 95  |     |     |  |
| 25 | Ser         | Asn          | Pro        | Pro        | Ile        | Ser         | Arg | Ser | Val | Leu | Asp | Gln | Ala | Ser | Cys |     |     |  |
|    |             |              |            | 100        |            |             |     |     | 105 |     |     |     |     | 110 |     |     |     |  |
| 30 | <210>       | 156          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211>       | 321          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212>       | DNA          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213>       | Mus musculus |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
| 35 | <400>       | 156          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | ggtgttgaag  | gagacattgt   | gatgacccag | tctcacaaat | tcatgtccac | atcagtagga  |     |     |     |     |     |     |     |     |     | 60  |     |  |
|    | gacaggggtca | gcatcacctg   | caaggccagt | caggatgtgg | gtactgctgt | agcctgggtat |     |     |     |     |     |     |     |     |     | 120 |     |  |
| 40 | caacagaaac  | cagggcaatc   | tcctaaacta | ctgatttact | gggcatccac | ccggcacact  |     |     |     |     |     |     |     |     |     | 180 |     |  |
|    | ggagtccctg  | atcgcttcac   | aggcagtgga | tctgggacag | atttcactct | caccattagc  |     |     |     |     |     |     |     |     |     | 240 |     |  |
|    | aatgtgcagt  | ctgaagactt   | ggcagattat | ttctgtcagc | aatatagcag | ctatcctctc  |     |     |     |     |     |     |     |     |     | 300 |     |  |
| 45 | acgttcggtg  | ctggaccaag   | c          |            |            |             |     |     |     |     |     |     |     |     |     | 321 |     |  |
| 50 | <210>       | 157          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211>       | 5            |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212>       | PRT          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213>       | Mus musculus |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
| 55 | <400>       | 157          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Asp         | Phe          | Trp        | Met        | Asn        |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | 1           |              |            |            | 5          |             |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <210>       | 158          |            |            |            |             |     |     |     |     |     |     |     |     |     |     |     |  |

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<211> 19  
<212> PRT  
<213> Mus musculus

5 <400> 158

Glu Ile Arg Leu Lys Ser Asn Asn Tyr Ala Thr His Tyr Ala Glu Ser  
1 5 10 15

10 Val Lys Gly

<210> 159  
<211> 13  
<212> PRT  
<213> Mus musculus

15 <400> 159

20 Leu Phe Tyr Tyr Tyr Asp Gly Thr Ser Gly Phe Ala Tyr  
1 5 10

<210> 160  
<211> 118  
<212> PRT  
<213> Mus musculus

25 <400> 160

30 Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Met Lys Val Ser Cys Val  
1 5 10 15

35 Ala Ser Gly Phe Ser Phe Ile Asp Phe Trp Met Asn Trp Val Arg Gln  
20 25 30

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

40 Asn Asn Tyr Ala Thr His Tyr Ala Glu Ser Val Lys Gly Arg Phe Thr  
50 55 60

45 Ile Ser Arg Asp Asp Ser Lys Ser Ser Val Tyr Leu Gln Met Asn Asn  
65 70 75 80

50 Leu Arg Pro Glu Asp Thr Gly Ile Tyr Tyr Cys Thr Ser Leu Phe Tyr  
85 90 95

Tyr Tyr Asp Gly Thr Ser Gly Phe Ala Tyr Trp Gly Gln Gly Thr Thr  
100 105 110

55 Val Thr Val Leu Leu Lys  
115

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<210> 161  
 <211> 17  
 <212> PRT  
 <213> Mus musculus

5

<400> 161

10

Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asp Gln Lys Asn Tyr Leu  
 1 5 10 15

Thr

15

<210> 162  
 <211> 7  
 <212> PRT  
 <213> Mus musculus

20

<400> 162

Trp Ala Ser Thr Arg Glu Ser  
 1 5

25

<210> 163  
 <211> 9  
 <212> PRT  
 <213> Mus musculus

30

<400> 163

Gln Asn Asp Tyr Asp Tyr Pro Leu Thr  
 1 5

35

<210> 164  
 <211> 109  
 <212> PRT  
 <213> Mus musculus

40

<400> 164

45

50

55

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|    |                    |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|----|--------------------|------------|------------|-------------|------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Asp                | Ile        | Val        | Met         | Thr        | Gln        | Ser | Pro | Ser | Ser | Leu | Thr | Val | Thr | Ala | Gly |     |
|    | 1                  |            |            |             | 5          |            |     |     |     | 10  |     |     |     |     | 15  |     |     |
| 5  | Glu                | Lys        | Val        | Thr         | Met        | His        | Cys | Lys | Ser | Ser | Gln | Ser | Leu | Leu | Asn | Ser |     |
|    |                    |            |            | 20          |            |            |     |     | 25  |     |     |     |     | 30  |     |     |     |
| 10 | Gly                | Asp        | Gln        | Lys         | Asn        | Tyr        | Leu | Thr | Trp | Tyr | Gln | Gln | Lys | Pro | Gly | Gln |     |
|    |                    |            | 35         |             |            |            |     | 40  |     |     |     |     | 45  |     |     |     |     |
| 15 | Pro                | Pro        | Lys        | Leu         | Leu        | Ile        | Tyr | Trp | Ala | Ser | Thr | Arg | Glu | Ser | Gly | Val |     |
|    |                    | 50         |            |             |            |            | 55  |     |     |     |     | 60  |     |     |     |     |     |
| 20 | Pro                | Asp        | Arg        | Phe         | Thr        | Gly        | Ser | Gly | Ser | Gly | Thr | Asp | Phe | Thr | Leu | Thr |     |
|    | 65                 |            |            |             |            | 70         |     |     |     |     | 75  |     |     |     |     | 80  |     |
| 25 | Ile                | Ser        | Ser        | Val         | Gln        | Ala        | Glu | Asp | Leu | Ala | Val | Tyr | Tyr | Cys | Gln | Asn |     |
|    |                    |            |            |             | 85         |            |     |     |     | 90  |     |     |     |     | 95  |     |     |
| 30 | Asp                | Tyr        | Asp        | Tyr         | Pro        | Leu        | Thr | Phe | Gly | Ala | Gly | Pro | Ser |     |     |     |     |
|    |                    |            |            | 100         |            |            |     |     | 105 |     |     |     |     |     |     |     |     |
|    | <210> 165          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 354          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> DNA          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 165          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
| 35 | ggaggaggct         | tggtgcaacc | tggaggatcc | atgaaagtct  | cctgtgttgc | ctctggattc |     |     |     |     |     |     |     |     |     |     | 60  |
|    | tctttcattg         | acttttggat | gaactgggtc | cgccagtctc  | cagagaaggg | gcttgagtgg |     |     |     |     |     |     |     |     |     |     | 120 |
|    | gttgctgaaa         | ttagattgaa | atctaataat | tatgcaacac  | attatgcgga | gtctgtgaaa |     |     |     |     |     |     |     |     |     |     | 180 |
| 40 | gggagggttca        | ccatctcaag | agatgattcc | aaaagtagtg  | tctacctgca | aatgaacaac |     |     |     |     |     |     |     |     |     |     | 240 |
|    | ttaagacctg         | aagacactgg | catttattac | tgtaccagcc  | tcttttatta | ctatgatggt |     |     |     |     |     |     |     |     |     |     | 300 |
| 45 | acttcgggggt        | ttgcttactg | gggccaaggg | accacgggtca | ccgttctcct | caaa       |     |     |     |     |     |     |     |     |     |     | 354 |
|    | <210> 166          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 327          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> DNA          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
| 50 | <213> Mus musculus |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 166          |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |
| 55 |                    |            |            |             |            |            |     |     |     |     |     |     |     |     |     |     |     |

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gacattgtga tgacacagtc tccgtcctcc ctgactgtga cagcaggaga gaaggtcact 60  
 atgcactgca agtccagtca gagtctttta aacagtggag atcaaaagaa ctacttgacc 120  
 5 tgggtaccagc agaaaccagg acagcctcct aaactgttga tctactgggc atccactcgg 180  
 gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240  
 atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatgattat 300  
 10 ccgctcacgt tcggtgctgg accaagc 327

<210> 167

<211> 5

15 <212> PRT

<213> Mus musculus

<400> 167

20 Asp Tyr Asn Met Asp  
 1 5

<210> 168

<211> 17

25 <212> PRT

<213> Mus musculus

<400> 168

30 Asp Ile Asn Pro Asn Tyr Asp Ser Thr Ser Tyr Asn Gln Lys Phe Lys  
 1 5 10 15

Gly

35 <210> 169  
 <211> 11

<212> PRT

<213> Mus musculus

40 <400> 169

Ser Arg Ser Tyr Asp Tyr Glu Gly Phe Ala Tyr  
 1 5 10

45 <210> 170  
 <211> 148

<212> PRT

<213> Mus musculus

50 <400> 170

55

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|    |       |              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|-------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Met   | Glu          | Trp | Ser | Gly | Val | Phe | Ile | Phe | Leu | Leu | Ser | Gly | Thr | Ala | Gly |  |
|    | 1     |              |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 5  | Val   | Leu          | Ser | Glu | Val | Gln | Leu | His | Gln | Phe | Gly | Ala | Glu | Leu | Val | Lys |  |
|    |       |              |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Pro   | Gly          | Ala | Ser | Val | Lys | Ile | Ser | Cys | Lys | Ala | Ser | Gly | Tyr | Thr | Phe |  |
|    |       |              | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
| 15 | Thr   | Asp          | Tyr | Asn | Met | Asp | Trp | Val | Lys | Gln | Ser | His | Gly | Lys | Ser | Leu |  |
|    |       | 50           |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |  |
| 20 | Glu   | Trp          | Ile | Gly | Asp | Ile | Asn | Pro | Asn | Tyr | Asp | Ser | Thr | Ser | Tyr | Asn |  |
|    | 65    |              |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 25 | Gln   | Lys          | Phe | Lys | Gly | Lys | Ala | Thr | Leu | Thr | Val | Asp | Lys | Ser | Ser | Ser |  |
|    |       |              |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| 30 | Thr   | Ala          | Tyr | Met | Glu | Leu | Arg | Ser | Leu | Thr | Ser | Glu | Asp | Thr | Ala | Val |  |
|    |       |              |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
| 35 | Tyr   | Tyr          | Cys | Ala | Arg | Ser | Arg | Ser | Tyr | Asp | Tyr | Glu | Gly | Phe | Ala | Tyr |  |
|    |       |              | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |  |
| 40 | Trp   | Gly          | Gln | Gly | Thr | Leu | Val | Thr | Val | Ser | Ala | Ala | Lys | Thr | Thr | Pro |  |
|    |       | 130          |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |  |
| 45 | Pro   | Ser          | Val | Tyr |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | 145   |              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 50 | <210> | 171          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> | 11           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> | PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> | Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 55 | <400> | 171          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 60 |       |              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Arg   | Ala          | Ser | Gly | Asn | Ile | His | Asn | Tyr | Leu | Ala |     |     |     |     |     |  |
|    | 1     |              |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     |     |  |
| 65 | <210> | 172          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> | 7            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> | PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> | Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 70 | <400> | 172          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 75 |       |              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | Asn   | Ala          | Lys | Thr | Leu | Ala | Asp |     |     |     |     |     |     |     |     |     |  |
|    | 1     |              |     |     | 5   |     |     |     |     |     |     |     |     |     |     |     |  |
| 80 | <210> | 173          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |

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<211> 8  
<212> PRT  
<213> Mus musculus

5 <400> 173

Gln His Phe Trp Ser Thr Leu Thr  
1 5

10 <210> 174  
<211> 139  
<212> PRT  
<213> Mus musculus

15 <400> 174

Met Ser Val Leu Thr Gln Val Leu Gly Leu Leu Leu Leu Trp Leu Thr  
1 5 10 15

20 Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser  
20 25 30

25 Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn  
35 40 45

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

Gln Leu Leu Val Tyr Asn Ala Lys Thr Leu Ala Asp Gly Val Pro Ser  
65 70 75 80

35 Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn  
85 90 95

40 Ser Leu Gln Pro Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp  
100 105 110

45 Ser Thr Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala  
115 120 125

Asp Ala Ala Pro Thr Val Ser Asn Pro Tyr Asp  
130 135

50 <210> 175  
<211> 444  
<212> DNA  
<213> Mus musculus

55 <400> 175

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atggaatgga gcggggtctt tatctttctc ctgtcaggaa ctgcaggtgt cctctctgag 60  
 gtccagctgc atcagtttgg agctgagctg gtgaagcctg gggcttcagt gaagatatcc 120  
 5 tgcaaggctt ctggctacac attcactgac tacaacatgg actgggtgaa gcagagccat 180  
 ggaaagagcc ttgagtggat tggagatatt aatcctaact atgatatgac tagctacaac 240  
 10 cagaagttca agggaaaggc cacattgact gtagacaagt cctccagcac agcctacatg 300  
 gagctccgca gcctgacatc tgaggacact gcagtctatt actgtgcaag atcgaggagc 360  
 15 tatgattacg aaggatttgc ttactggggc caagggactc tggtcactgt ctctgcagcc 420  
 aaaacaacac ccccatcagt ctat 444

<210> 176  
 <211> 444  
 20 <212> DNA  
 <213> Mus musculus

<400> 176  
 25 atggaatgga gcggggtctt tatctttctc ctgtcaggaa ctgcaggtgt cctctctgag 60  
 gtccagctgc atcagtttgg agctgagctg gtgaagcctg gggcttcagt gaagatatcc 120  
 30 tgcaaggctt ctggctacac attcactgac tacaacatgg actgggtgaa gcagagccat 180  
 ggaaagagcc ttgagtggat tggagatatt aatcctaact atgatatgac tagctacaac 240  
 cagaagttca agggaaaggc cacattgact gtagacaagt cctccagcac agcctacatg 300  
 35 gagctccgca gcctgacatc tgaggacact gcagtctatt actgtgcaag atcgaggagc 360  
 tatgattacg aaggatttgc ttactggggc caagggactc tggtcactgt ctctgcagcc 420  
 aaaacaacac ccccatcagt ctat 444

40 <210> 177  
 <211> 11  
 <212> PRT  
 45 <213> Mus musculus  
 <400> 177

50 Leu Trp Ser Val Asn Gln Lys Asn Tyr Leu Ser  
 1 5 10

<210> 178  
 <211> 7  
 <212> PRT  
 55 <213> Mus musculus  
 <400> 178

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Gly Ala Ser Ile Arg Glu Ser  
1 5

<210> 179  
<211> 9  
<212> PRT  
<213> Mus musculus

<400> 179

Gln His Asn His Gly Ser Phe Leu Pro  
1 5

<210> 180  
<211> 139  
<212> PRT  
<213> Mus musculus

<400> 180

Met Ser Val Leu Thr Gln Val Leu Gly Leu Leu Leu Trp Leu Thr  
1 5 10 15

Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser  
20 25 30

Ala Ser Val Gly Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn  
35 40 45

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

Gln Leu Leu Val Tyr Asn Ala Lys Thr Leu Ala Asp Gly Val Pro Ser  
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn  
85 90 95

Ser Leu Gln Pro Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp  
100 105 110

Ser Thr Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala  
115 120 125

Asp Ala Ala Pro Thr Val Ser Asn Pro Tyr Asp  
130 135

<210> 181  
<211> 398  
<212> DNA  
<213> Mus musculus

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<400> 181

|    |             |            |            |            |            |            |     |
|----|-------------|------------|------------|------------|------------|------------|-----|
| 5  | gcgggtcctgc | ggtgctctag | aggactacta | gtcatatgga | tttccgatat | ccagctgacc | 60  |
|    | cagtctccat  | cctccctggc | tgtgacagca | ggagagaagg | tcactatgag | ctgcaagtcc | 120 |
|    | agtcagagtc  | ttttgtggag | tgtaaaccag | aagaactact | tgtcctggta | ccagcagaaa | 180 |
| 10 | caaaggcagc  | ctcctaaact | gcttatctat | ggggcatcca | ttagagaatc | ttgggtccct | 240 |
|    | gatcggttca  | caggaagtgg | atctgggaca | gacttcactc | tcaccattag | caatgtgcat | 300 |
|    | gctgaagacc  | tagcagttta | ttactgtcaa | cacaatcatg | gcagctttct | cccctcacgt | 360 |
| 15 | tcggagcagg  | taccaagctg | gagatcaaac | aatcggat   |            |            | 398 |

<210> 182

 $\langle 211 \rangle$  11

20 <212> PRT

<213> Mus musculus

<400> 182

25 Arg Ala Ser Gly Asn Ile His Asn Tyr Leu Ala  
1 5 10

<210> 183

 $\langle 211 \rangle$  7

30 <212> PRT

<213> Mus musculus

<400> 183

35                           Asn Ala Lys Thr Leu Ala Asp  
                               1                           5

<210> 184

<211> 9

40 <212> PRT

<213> Mus musculus

<400> 184

45                    Gln His Phe Trp Ser Thr Leu Thr Phe  
                       1                    5

<210> 185

<211> 117

50 <212> PRT

<213> Mus musculus

<400> 185

55

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|    |                                                                        |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Arg                                                                    | Thr | Thr | Ser | His | Met | Asp | Ser | Asp | Ile | Gln | Leu | Thr | Gln | Ser | Pro |  |
|    | 1                                                                      |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 5  | Ala                                                                    | Ser | Leu | Ser | Ala | Ser | Val | Gly | Glu | Thr | Val | Thr | Ile | Thr | Cys | Arg |  |
|    |                                                                        |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 10 | Ala                                                                    | Ser | Gly | Asn | Ile | His | Asn | Tyr | Leu | Ala | Trp | Tyr | Gln | Gln | Lys | Gln |  |
|    |                                                                        |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |
|    | Gly                                                                    | Lys | Ser | Pro | Gln | Leu | Leu | Val | Tyr | Asn | Ala | Lys | Thr | Leu | Ala | Asp |  |
|    |                                                                        | 50  |     |     |     | 55  |     |     |     |     |     | 60  |     |     |     |     |  |
| 15 | Gly                                                                    | Val | Pro | Ser | Arg | Phe | Ser | Gly | Ser | Gly | Ser | Gly | Thr | Gln | Tyr | Ser |  |
|    | 65                                                                     |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |  |
| 20 | Leu                                                                    | Lys | Ile | Asn | Ser | Leu | Gln | Pro | Glu | Asp | Phe | Gly | Ser | Tyr | Tyr | Cys |  |
|    |                                                                        |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
|    | Gln                                                                    | His | Phe | Trp | Ser | Thr | Leu | Thr | Phe | Gly | Gly | Gly | Thr | Lys | Leu | Glu |  |
| 25 |                                                                        |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |  |
|    | Ile                                                                    | Lys | Gln | Ser | Asp |     |     |     |     |     |     |     |     |     |     |     |  |
|    |                                                                        |     |     | 115 |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 30 | <210> 186                                                              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> 353                                                              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> DNA                                                              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> Mus musculus                                                     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 35 | <400> 186                                                              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | gaggactact agtcatatgg attccgatat ccagctgacc cagtctccag cctccctatc 60   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 40 | tgcatctgtg ggagaaactg tcaccatcac atgtcgagca agtggaata ttcacaatta 120   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | tttagcatgg tatcagcaga aacagggaaa atctcctcag ctccctgttct ataatgcaaa 180 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | aaccttagca gatggtgtgc catcaagggt cagtggcagt ggatcaggaa cacaatattc 240  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 45 | tctcaagatc aacagcctgc agcctgaaga ttttgggagt tattactgtc aacatttttg 300  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | gagtacgctc acgttcggag gtggtaccaa gctggagatc aaacaatcgg atc 353         |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <210> 187                                                              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 50 | <211> 11                                                               |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> PRT                                                              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> Mus musculus                                                     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |

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<210> 188  
 <211> 7  
 <212> PRT  
 <213> Mus musculus

5

<400> 188

Tyr Ala Ser Gln Ser Ile Ser  
 1 5

10

<210> 189  
 <211> 9  
 <212> PRT  
 <213> Mus musculus

15

<400> 189

Gln Gln Ser Asn Ser Trp Pro Tyr Thr  
 1 5

20

<210> 190  
 <211> 94  
 <212> PRT  
 <213> Mus musculus

25

<400> 190

Ser Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser  
 1 5 10 15

30

Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu  
 20 25 30

35

Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe  
 35 40 45

40

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val  
 50 55 60

45

Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp  
 65 70 75 80

Pro Tyr Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys Gln  
 85 90

50

<210> 191  
 <211> 283  
 <212> DNA  
 <213> Mus musculus

55

<400> 191

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tcaggagata gagtcagtct ttcctgcagg gccagtcaaa gtattagcaa ctacctacac 60  
 tggatatcaac aaaaatcaca tgagtctcca aggcttctca tcaagtatgc ttcccagtc 120  
 5 atctctggga tcccctccag gttcagtggc agtggatcag ggacagattt cactctcagt 180  
 atcaacagtg tggagactga agattttgga atgtatttct gtcaacagag taacagctgg 240  
 ccgtacacgt tcggtgcagg taccaagctg gagatcaaac aga 283

10  
 <210> 192  
 <211> 11  
 <212> PRT  
 <213> Mus musculus

15  
 <400> 192

20  
 Leu Ser Ile Val Asn Arg Tyr His Tyr Met Ser  
 1 5 10

<210> 193  
 <211> 6  
 <212> PRT  
 <213> Mus musculus

25  
 <400> 193

30  
 Glu Ala Ser Ile Thr Lys  
 1 5

<210> 194  
 <211> 9  
 <212> PRT  
 <213> Mus musculus

35  
 <400> 194

40  
 Gln His Asn Arg Gly Ser Phe Leu Pro  
 1 5

<210> 195  
 <211> 105  
 <212> PRT  
 <213> Mus musculus

45  
 <400> 195

50

55

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|    |                    |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|----|--------------------|-------------|------------|------------|-------------|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Gly                | Leu         | Phe        | Cys        | Ser         | Val        | Glu | Arg | Cys | His | Tyr | Gln | Leu | Gln | Ser | Ser |     |  |
|    | 1                  |             |            |            | 5           |            |     |     |     | 10  |     |     |     |     | 15  |     |     |  |
| 5  |                    | Gln         | Asn        | Leu        | Leu         | Ser        | Ile | Val | Asn | Arg | Tyr | His | Tyr | Met | Ser | Gly | Asn |  |
|    |                    |             |            | 20         |             |            |     |     | 25  |     |     |     |     | 30  |     |     |     |  |
| 10 | Pro                | Pro         | Lys        | Leu        | Leu         | Val        | Tyr | Pro | Ala | Leu | Leu | Ile | Tyr | Glu | Ala | Ser |     |  |
|    |                    |             | 35         |            |             |            |     | 40  |     |     |     |     | 45  |     |     |     |     |  |
| 15 | Ile                | Thr         | Lys        | Ser        | Cys         | Val        | Pro | Asp | Arg | Phe | Thr | Arg | Ser | Gly | Ser | Gly |     |  |
|    |                    | 50          |            |            |             |            | 55  |     |     |     |     | 60  |     |     |     |     |     |  |
| 20 | Thr                | Asn         | Phe        | Thr        | Leu         | Thr        | Ile | Asn | Phe | Val | His | Ala | Asp | Asp | Leu | Ile |     |  |
|    | 65                 |             |            |            |             | 70         |     |     |     |     | 75  |     |     |     | 80  |     |     |  |
| 25 | Phe                | Tyr         | Tyr        | Cys        | Gln         | His        | Asn | Arg | Gly | Ser | Phe | Leu | Pro | Ser | Ser | Ser |     |  |
|    |                    |             |            | 85         |             |            |     |     |     | 90  |     |     |     |     | 95  |     |     |  |
| 30 | Val                | Gln         | Val        | Pro        | Arg         | Arg        | Arg | Ser | Asn |     |     |     |     |     |     |     |     |  |
|    |                    |             |            | 100        |             |            |     |     | 105 |     |     |     |     |     |     |     |     |  |
|    | <210> 196          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> 317          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> DNA          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> Mus musculus |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <400> 196          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
| 35 | ggactcttct         | gctctgtgga  | gagatgtcac | tatcaactgc | aatccagtca  | gaatcttttg |     |     |     |     |     |     |     |     |     |     | 60  |  |
|    | agtattgtaa         | accggtatca  | ctacatgtcc | ggaaaccctc | ctaaactcct  | ggtctatcct |     |     |     |     |     |     |     |     |     |     | 120 |  |
|    | gcactgctta         | tctatgaggc  | atccattaca | aatcctgtg  | tccctgatcg  | gttcacacga |     |     |     |     |     |     |     |     |     |     | 180 |  |
| 40 | agtggatctg         | ggacaaaactt | cactctcacc | attaattttg | tgcattgctga | tgacctaat  |     |     |     |     |     |     |     |     |     |     | 240 |  |
|    | ttttattact         | gtcaacacaa  | tcgtggcagc | tttctcccct | caagttcggg  | gcaggtacca |     |     |     |     |     |     |     |     |     |     | 300 |  |
|    | agaaggagat         | caaacaa     |            |            |             |            |     |     |     |     |     |     |     |     |     |     | 317 |  |
| 45 | <210> 197          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> 5            |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> PRT          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> Mus musculus |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
| 50 | <400> 197          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
| 55 |                    | Gly         | Tyr        | Thr        | Met         | Asn        |     |     |     |     |     |     |     |     |     |     |     |  |
|    |                    | 1           |            |            | 5           |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <210> 198          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> 16           |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> PRT          |             |            |            |             |            |     |     |     |     |     |     |     |     |     |     |     |  |

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<213> Mus musculus

<400> 198

5           Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys  
          1                   5                   10                   15

<210> 199

<211> 9

10       <212> PRT

<213> Mus musculus

<400> 199

15                   Trp Gly Val Trp Ser Ala Met Asp Tyr  
                  1                   5

<210> 200

<211> 100

20       <212> PRT

<213> Mus musculus

<400> 200

25           Asp Ile Leu Gln Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Thr Met Asn  
          1                   5                   10                   15

30           Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Ile Gly Leu Ile  
                  20                   25                   30

35           Asn Pro Tyr Asn Gly Gly Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys  
                  35                   40                   45

40           Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu  
                  50                   55                   60

45           Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Trp  
          65                   70                   75                   80

50           Gly Val Trp Ser Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr  
                  85                   90                   95

                  Val Ser Ser Lys  
                          100

55       <210> 201

<211> 11

<212> PRT

<213> Mus musculus

<400> 201

          Lys Ala Ser Gln Asn Val Arg Thr Ala Val Ala  
          1                   5                   10

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<210> 202  
 <211> 7  
 <212> PRT  
 <213> Mus musculus

5

<400> 202

Leu Ala Ser Asn Arg Asp Thr  
 1 5

10

<210> 203  
 <211> 9  
 <212> PRT  
 <213> Mus musculus

15

<400> 203

Leu Gln His Cys Asn Tyr Pro Asn Glu  
 1 5

20

<210> 204  
 <211> 90  
 <212> PRT  
 <213> Mus musculus

25

<400> 204

Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asn Val Arg Thr Ala  
 1 5 10 15

30

Val Ala Trp Tyr Gln Gln Lys Pro Arg Gln Ser Pro Lys Ala Leu Ile  
 20 25 30

35

Tyr Leu Ala Ser Asn Arg Asp Thr Gly Leu Pro Asp Arg Phe Pro Gly  
 35 40 45

40

Arg Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile Thr Asn Val Gln Ser  
 50 55 60

45

Glu Asp Leu Glu Asp Tyr Phe Cys Leu Gln His Cys Asn Tyr Pro Asn  
 65 70 75 80

Glu Phe Arg Gly Cys Thr Lys Val Pro Ile  
 85 90

50

<210> 205  
 <211> 301  
 <212> DNA  
 <213> Mus musculus

55

<400> 205

EP 2 740 489 B1

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 agccatggaa agaaccttga gtggattgga cttattaatc cttacaatgg tgggtactagc 120  
 5 tacaaccaga agttcaaggg caaggccaca ttaactgtag acaagtcac cagcacagcc 180  
 tacatggagc tcctcagtct gacatctgag gactctgcag tctattactg tgcaagatgg 240  
 10 ggggtatggt cggctatgga ctactggggc caagggacca cggtcaccgt ctcctcaaaa 300  
 a 301

<210> 206  
 <211> 290  
 15 <212> DNA  
 <213> Mus musculus

<400> 206  
 20 gacaggggtca gcatcacctg caaggccagt caaaatgttc gtactgctgt agcctgggtat 60  
 caacagaaac cacggcagtc tcctaaagca ctgatttact tggcatccaa ccgggacact 120  
 ggactccctg atcgcttccc aggcagggga tctgggacag atttcactct caacattacc 180  
 25 aatgtgcaat ctgaagacct ggaagattat ttctgtctgc aacattgtaa ttatcctaac 240  
 gagttcagag gttgtaccaa ggtgccaatc taaagaacaa acaccccctg 290

30 <210> 207  
 <211> 5  
 <212> PRT  
 <213> Mus musculus

35 <400> 207

Ser Tyr Trp Met Gln  
 1 5

40 <210> 208  
 <211> 17  
 <212> PRT  
 <213> Mus musculus

45 <400> 208

Ala Ile Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe Lys  
 1 5 10 15

50 Gly

<210> 209  
 <211> 11  
 55 <212> PRT  
 <213> Mus musculus

<400> 209

EP 2 740 489 B1

Ala Arg Gly Glu Tyr Gly Asn Tyr Phe Ala Tyr  
1 5 10

<210> 210  
<211> 116  
<212> PRT  
<213> Mus musculus

<400> 210

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

Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Met Gln  
20 25 30

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

Tyr Pro Gly Asp Gly Asp Thr Arg Tyr Thr Gln Lys Phe Lys Gly Lys  
50 55 60

Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu  
65 70 75 80

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

Glu Tyr Gly Asn Tyr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr  
100 105 110

Val Ser Ser Asn  
115

<210> 211  
<211> 11  
<212> PRT  
<213> Mus musculus

<400> 211

Lys Ala Ser Gln Asp Ile Asn Ser Tyr Leu Ser  
1 5 10

<210> 212  
<211> 7  
<212> PRT  
<213> Mus musculus

<400> 212

# EP 2 740 489 B1

Arg Ala Asn Arg Leu Val Asp  
1 5

5  
<210> 213  
<211> 9  
<212> PRT  
<213> Mus musculus

10  
<400> 213

Leu Gln Tyr Asp Glu Phe Pro Leu Thr  
1 5

15  
<210> 214  
<211> 100  
<212> PRT  
<213> Mus musculus

20  
<400> 214

Thr Ser Asp Ala Ser Leu Gly Glu Arg Val Thr Ile Thr Cys Lys Ala  
1 5 10 15

25  
Ser Gln Asp Ile Asn Ser Tyr Leu Ser Trp Phe Gln Gln Lys Pro Gly  
20 25 30

30  
Lys Ser Pro Lys Thr Leu Ile Tyr Arg Ala Asn Arg Leu Val Asp Gly  
35 40 45

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

35  
Thr Ile Ser Ser Leu Glu Tyr Glu Asp Met Gly Ile Tyr Tyr Cys Leu  
65 70 75 80

40  
Gln Tyr Asp Glu Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu  
85 90 95

45  
Ile Lys Gln Lys  
100

<210> 215  
<211> 352  
<212> DNA  
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<213> Mus musculus

<400> 215

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aggcttcttg ctacaccttt actagctact ggatgcagtg ggtaaaacag aggcctggac 120  
agggtctgga atggattggg gctattttatc ctggagatgg tgatactagg tacactcaga 180

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agttcaaggg caaggccaca ttgactgcag ataaatcctc cagcacagcc tacatgcaac 240  
 tcagcagctt ggcattctgag gactctgcgg tctattactg tgcaagaggg gagtatggta 300  
 5 actatitttgc ttactggggc caagggacca cggtcaccgt ctctctcaat cg 352

<210> 216

<211> 302

<212> DNA

10 <213> Mus musculus

<400> 216

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 atcgtgcaaaa cagattggta gatgggggtcc catcaagggt cagtggcagt ggatctgggc 180  
 20 aagattattc tctcaccatc agcagcctgg agtatgaaga tatgggaatt tattattgtc 240  
 tacagtatga tgagtttccg ctcacgttcg gaggaggtac caagctggag atcaaacaaa 300  
 aa 302

<210> 217

<211> 5

<212> PRT

<213> Mus musculus

30 <400> 217

Asp Thr Tyr Met His  
 1 5

<210> 218

<211> 17

<212> PRT

<213> Mus musculus

40 <400> 218

Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro Lys Phe Gln  
 1 5 10 15

Gly

<210> 219

<211> 14

<212> PRT

<213> Mus musculus

<400> 219

Ala Arg Pro Ile His Tyr Tyr Tyr Gly Ser Ser Leu Ala Tyr  
 1 5 10

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<210> 220  
 <211> 108  
 <212> PRT  
 <213> Mus musculus

5

<400> 220

10

Ala Trp Leu Ser Gln Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys  
 1 5 10 15

15

Asp Thr Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu  
 20 25 30

20

Trp Ile Gly Arg Ile Asp Pro Ala Asn Gly Asn Thr Lys Tyr Asp Pro  
 35 40 45

25

Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr  
 50 55 60

Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr  
 65 70 75 80

30

Tyr Cys Ala Arg Pro Ile His Tyr Tyr Tyr Gly Ser Ser Leu Ala Tyr  
 85 90 95

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Lys  
 100 105

35

<210> 221  
 <211> 11  
 <212> PRT  
 <213> Mus musculus

40

<400> 221

Ser Val Asp Ser Tyr Gly Asn Ser Phe Met His  
 1 5 10

45

<210> 222  
 <211> 7  
 <212> PRT  
 <213> Mus musculus

50

<400> 222

Arg Ala Ser Asn Leu Glu Ser  
 1 5

55

<210> 223  
 <211> 9  
 <212> PRT  
 <213> Mus musculus

# EP 2 740 489 B1

<400> 223

Gln Gln Ser Asn Glu Asp Pro Gly Arg  
1 5

5

<210> 224

<211> 104

<212> PRT

<213> Mus musculus

10

<400> 224

Glu Phe His Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg  
1 5 10 15

15

Ala Ser Glu Ser Val Asp Ser Tyr Gly Asn Ser Phe Met His Trp Tyr  
20 25 30

20

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser  
35 40 45

25

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

30

Thr Asp Phe Thr Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala  
65 70 75 80

Thr Tyr Tyr Cys Gln Gln Ser Asn Glu Asp Pro Gly Arg Ser Glu Val  
85 90 95

35

Val Pro Ser Trp Arg Ser Asn Lys  
100

<210> 225

40

<211> 326

<212> DNA

<213> Mus musculus

<400> 225

45

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cactgggtga agcagaggcc tgaacagggc ctggagtgga ttggaaggat tgatcctgcg 120

50

aatggtaata ctaaatatga cccgaagttc cagggcaagg ccactataac agcagacaca 180

tcctccaaca cagcctacct gcagctcagc agcctgacat ctgaggacac tgccgtctat 240

tactgtgcta gaccgattca ttattactac ggtagtagcc ttgcttactg gggccaaggg 300

55

accacgggtca ccgtctcctc aaaaaa 326

<210> 226

# EP 2 740 489 B1

<211> 313  
 <212> DNA  
 <213> Mus musculus

5 <400> 226

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gagtttcatg ctgtgtctct agggcagagg gccaccatat cctgcagagc cagtgaaagt      60
10 gttgatagtt atggcaatag ttttatgcac tgggtaccagc agaaaccagg acagccaccc      120

aaactcctca tctatcgtgc atccaaccta gaatctggga tccctgccag gttcagtggc      180
15 agtgggtcta ggacagactt caccctcacc attaatcctg tggaggctga tgatgttgca      240

acctattact gtcagcaaag taatgaggat cctggacggt cggaggtggt accaagctgg      300

agatcaaaca aaa      313
  
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 <213> Mus musculus

25 <400> 227

Asp Tyr Tyr Met Ser  
 1 5

30 <210> 228  
 <211> 17  
 <212> PRT  
 <213> Mus musculus

35 <400> 228

Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys  
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40 Gly

<210> 229  
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<400> 229

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 1 5

<210> 230  
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<400> 230

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Pro Arg Ala Ser Leu Gly Val Ser Glu Thr Leu Leu Cys Thr Ser Gly  
1 5 10 15

5 Phe Thr Phe Thr Asp Tyr Tyr Met Ser Trp Val Arg Gln Pro Pro Gly  
20 25 30

10 Lys Ala Leu Glu Trp Leu Gly Phe Ile Arg Asn Lys Ala Asn Gly Tyr  
35 40 45

15 Thr Thr Glu Tyr Ser Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg  
50 55 60

20 Asp Asn Ser Gln Ser Ile Leu Tyr Leu Gln Met Asn Thr Leu Arg Ala  
65 70 75 80

Glu Asp Ser Ala Thr Tyr Tyr Cys Ala Arg Ala Asn Trp Ala Phe Asp  
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25 Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Lys  
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<210> 231  
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30 <213> Mus musculus

<400> 231

35 Arg Ala Ser Gln Ser Ile Ser Asn Tyr Leu His  
1 5 10

<210> 232  
<211> 7  
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40 <213> Mus musculus

<400> 232

45 Tyr Ala Ser Gln Ser Ile Ser  
1 5

<210> 233  
<211> 9  
<212> PRT  
50 <213> Mus musculus

<400> 233

55 Gln Gln Ser Asn Ser Trp Pro Tyr Thr  
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<210> 234  
<211> 94

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<212> PRT

<213> Mus musculus

<400> 234

5

Ser Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser  
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10

Asn Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu  
20 25 30

15

Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe  
35 40 45

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val  
50 55 60

20

Glu Thr Glu Asp Phe Gly Met Tyr Phe Cys Gln Gln Ser Asn Ser Trp  
65 70 75 80

25

Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gln  
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<210> 235

<211> 329

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<212> DNA

<213> Mus musculus

<400> 235

35

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40

ttattagaaa caaagcta at ggttacacaa cagagtacag tgcattctgtg aagggtcggg 180

tcaccatctc cagagataat tcccaaagca tcctctatct tcaaataaac accctgagag 240

ctgaggacag tgccacttat tactgtgcaa gggctaactg ggcctttgac tactggggcc 300

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<210> 236

<211> 284

<212> DNA

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<213> Mus musculus

<400> 236

55

# EP 2 740 489 B1

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 5 atctctggga tcccctccag gttcagtggc agtggatcag ggacagattt cactctcagt 180  
 atcaacagtg tggagactga agatttttga atgtatttct gtcaacagag taacagctgg 240  
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10  
 <210> 237  
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15  
 <400> 237

20  
 Asp Tyr Tyr Met Ser  
 1 5

<210> 238  
 <211> 17  
 <212> PRT  
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25  
 <400> 238

30  
 Arg Asn Lys Ala Asn Gly Tyr Thr Thr Glu Tyr Ser Ala Ser Val Lys  
 1 5 10 15

Gly

35  
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40  
 <400> 239

Ala Arg Ala Pro Leu Leu Tyr Tyr Ala Met Asp Tyr  
 1 5 10

45  
 <210> 240  
 <211> 111  
 <212> PRT  
 <213> Mus musculus

50  
 <400> 240

55

# EP 2 740 489 B1

|    |                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Pro                | Ala | Cys | Leu | Pro | Gly | Gly | Ser | Leu | Arg | Leu | Ser | Cys | Ala | Thr | Ser |
|    | 1                  |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| 5  | Gly                | Phe | Thr | Phe | Thr | Asp | Tyr | Tyr | Met | Ser | Trp | Val | Arg | Gln | Pro | Pro |
|    |                    |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| 10 | Gly                | Lys | Ala | Leu | Glu | Trp | Leu | Gly | Phe | Ile | Arg | Asn | Lys | Ala | Asn | Gly |
|    |                    |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| 15 | Tyr                | Thr | Thr | Glu | Tyr | Ser | Ala | Ser | Val | Lys | Gly | Arg | Phe | Thr | Ile | Ser |
|    |                    | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| 20 | Arg                | Asp | Asn | Ser | Gln | Ser | Ile | Leu | Tyr | Leu | Gln | Met | Asn | Thr | Leu | Arg |
|    | 65                 |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| 25 | Ala                | Glu | Asp | Ser | Ala | Thr | Tyr | Tyr | Cys | Ala | Arg | Ala | Pro | Leu | Leu | Tyr |
|    |                    |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| 30 | Tyr                | Ala | Met | Asp | Tyr | Trp | Gly | Gln | Gly | Thr | Thr | Val | Thr | Val | Ser |     |
|    |                    |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
|    | <210> 241          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 11           |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 241          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 35 |                    |     |     | Asn | Val | Ser | Thr | Ser | Gly | Tyr | Ser | Tyr | Met | His |     |     |
|    |                    |     |     | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |
| 40 | <210> 242          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 7            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 242          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 45 |                    |     |     |     | Leu | Val | Ser | Asn | Leu | Glu | Ser |     |     |     |     |     |
|    |                    |     |     |     | 1   |     |     |     | 5   |     |     |     |     |     |     |     |
| 50 | <210> 243          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 8            |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <213> Mus musculus |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <400> 243          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 55 |                    |     |     |     | Gln | His | Ile | Arg | Glu | Leu | Thr | Arg |     |     |     |     |
|    |                    |     |     |     | 1   |     |     |     | 5   |     |     |     |     |     |     |     |
|    | <210> 244          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|    | <211> 102          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

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<212> PRT

<213> Mus musculus

<400> 244

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Arg Leu Pro Phe Tyr Ser Leu Glu Gln Arg Ala Thr Ile Ser Tyr Arg  
1 5 10 15

10

Ala Ser Lys Asn Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn  
20 25 30

15

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Val Ser  
35 40 45

20

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

Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala  
65 70 75 80

25

Thr Tyr Tyr Cys Gln His Ile Arg Glu Leu Thr Arg Ser Glu Leu Val  
85 90 95

30

Pro Ser Trp Lys Ser Asn  
100

<210> 245

<211> 340

<212> DNA

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<213> Mus musculus

<400> 245

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actgattact acatgagctg ggtccgccag cctccaggaa aggcaactga gtgggtgggt 120

tttattagaa acaaagctaa tggttacaca acagagtaca gtgcatctgt gaagggtcgg 180

45

ttcaccatct ccagagataa ttcccaaagc atcctctatc ttcaaataaa caccctgaga 240

gctgaggaca gtgccactta ttactgtgca agagcccctc tactttacta tgctatggac 300

tactggggcc aagggaccac ggtcaccgtc tcctaaatta 340

50

<210> 246

<211> 306

<212> DNA

<213> Mus musculus

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<400> 246

# EP 2 740 489 B1

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 5 aaactcctca tctatcttgt atccaaccta gaatctgggg tccctgccag gttcagtggc 180  
 agtgggtctg ggacagactt caccctcaac atccatcctg tggaggagga ggatgctgca 240  
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 10 tcaaac 306

<210> 247  
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 15 <212> PRT  
 <213> Mus musculus

<400> 247

20 Ser Tyr Trp Met His  
 1 5

<210> 248  
 <211> 17  
 25 <212> PRT  
 <213> Mus musculus

<400> 248

30 Met Ile Asp Pro Ser Asn Ser Glu Thr Arg Leu Asn Gln Lys Phe Lys  
 1 5 10 15

35 Asp

<210> 249  
 <211> 12  
 <212> PRT  
 <213> Mus musculus

40 <400> 249

45 Ala Arg Gly Leu Arg His Tyr Trp Tyr Phe Asp Val  
 1 5 10

<210> 250  
 <211> 101  
 <212> PRT  
 <213> Mus musculus

50 <400> 250

55

EP 2 740 489 B1

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

<210> 251  
 <211> 11  
 <212> PRT  
 <213> Mus musculus  
 <400> 251

|    |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Ser | Val | Ser | Thr | Ser | Gly | Tyr | Ser | Tyr | Met | His |
| 35 | 1   |     |     |     | 5   |     |     |     |     | 10  |     |

<210> 252  
 <211> 7  
 <212> PRT  
 <213> Mus musculus  
 <400> 252

|    |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|
|    | Leu | Val | Ser | Asn | Leu | Glu | Ser |
| 45 | 1   |     |     |     | 5   |     |     |

<210> 253  
 <211> 9  
 <212> PRT  
 <213> Mus musculus  
 <400> 253

|    |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Gln | His | Ile | Arg | Glu | Leu | Thr | Arg | Ser |
| 55 | 1   |     |     |     | 5   |     |     |     |     |

<210> 254  
 <211> 99

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<212> PRT

<213> Mus musculus

<400> 254

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Thr Ile Leu Trp Arg Glu Gly Pro Phe Ser Tyr Arg Ala Ser Lys Ser  
1 5 10 15

10

Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro  
20 25 30

15

Gly Gln Pro Pro Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser  
35 40 45

20

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr  
50 55 60

Leu Asn Ile His Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys  
65 70 75 80

25

Gln His Ile Arg Glu Leu Thr Arg Ser Glu Glu Val Pro Ser Trp Arg  
85 90 95

Ser Asn Lys

30

<210> 255

<211> 304

<212> DNA

<213> Mus musculus

35

<400> 255

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ttaaatacaga agttcaagga caaggccaca ttgaatgtag acaaatacctc caacacagcc 180

45

tacatgcagc tcagcagcct gacatctgag gactctgcag tctattactg tgcaagaggg 240

ttacgccact actggtactt cgatgtctgg ggccaaggga ccacgggtcac cgtctcctca 300

aaaa 304

50

<210> 256

<211> 298

<212> DNA

<213> Mus musculus

55

<400> 256

# EP 2 740 489 B1

|    |                                                                    |     |
|----|--------------------------------------------------------------------|-----|
|    | actattctct ggagagaggg ccccttctca tacagggcca gcaaaagtgt cagtacatct  | 60  |
|    | ggctatagtt atatgcaactg gaaccaacag aaaccaggac agccacccag actcctcatc | 120 |
| 5  | tatcttgtat ccaacctaga atctggggtc cctgccaggt tcagtggcag tgggtctggg  | 180 |
|    | acagacttca ccctcaacat ccattcctgtg gaggaggagg atgctgcaac ctattactgt | 240 |
| 10 | cagcacatta gggagcttac acgttcggag gaggtaccaa gctggagatc aaacaaaa    | 298 |

|    |                                                    |    |
|----|----------------------------------------------------|----|
| 15 | <210> 257<br><211> 22<br><212> DNA<br><213> primer |    |
| 20 | <400> 257<br>aggtsharct gcagsagtow gg              | 22 |
| 25 | <210> 258<br><211> 34<br><212> DNA<br><213> primer |    |
| 30 | <400> 258<br>tgaggagacg gtgassgtgg tcccttgcc ccag  | 34 |
| 35 | <210> 259<br><211> 27<br><212> DNA<br><213> primer |    |
| 40 | <400> 259<br>tccgatatcc agctgaccca gtctcca         | 27 |
| 45 | <210> 260<br><211> 31<br><212> DNA<br><213> primer |    |
| 50 | <400> 260<br>gttgatctc cagcttgga cchscdcca a       | 31 |
| 55 | <210> 261<br><211> 15<br><212> DNA<br><213> primer |    |
|    | <400> 261<br>agtcacgacg ttgta                      | 15 |
|    | <210> 262<br><211> 15<br><212> DNA<br><213> primer |    |
|    | <400> 262                                          |    |

# EP 2 740 489 B1

caggaaacag ctatgac 17

<210> 263

<211> 240

<212> DNA

<213> Gallus gallus

<400> 263

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15 aaggggggggt ctgcgggctc tatggggggg tcaacggggg gtctcacggg gggccggctc 180  
cgcgaggccg tgtggcggcg gctccgtcag cgctttctgt ccttccccac agggcgcgcc 240

<210> 264

<211> 330

<212> PRT

<213> Homo sapiens

<400> 264

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|    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|    | Ala | Ser | Thr | Lys | Gly | Pro | Ser | Val | Phe | Pro | Leu | Ala | Pro | Ser | Ser | Lys |
|    | 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| 5  | Ser | Thr | Ser | Gly | Gly | Thr | Ala | Ala | Leu | Gly | Cys | Leu | Val | Lys | Asp | Tyr |
|    |     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| 10 | Phe | Pro | Glu | Pro | Val | Thr | Val | Ser | Trp | Asn | Ser | Gly | Ala | Leu | Thr | Ser |
|    |     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| 15 | Gly | Val | His | Thr | Phe | Pro | Ala | Val | Leu | Gln | Ser | Ser | Gly | Leu | Tyr | Ser |
|    | 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| 20 | Leu | Ser | Ser | Val | Val | Thr | Val | Pro | Ser | Ser | Ser | Leu | Gly | Thr | Gln | Thr |
|    | 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| 25 | Tyr | Ile | Cys | Asn | Val | Asn | His | Lys | Pro | Ser | Asn | Thr | Lys | Val | Asp | Lys |
|    |     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |
| 30 | Lys | Val | Glu | Pro | Lys | Ser | Cys | Asp | Lys | Thr | His | Thr | Cys | Pro | Pro | Cys |
|    |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |
| 35 | Pro | Ala | Pro | Glu | Leu | Leu | Gly | Gly | Pro | Ser | Val | Phe | Leu | Phe | Pro | Pro |
|    |     |     |     | 115 |     |     |     | 120 |     |     |     |     | 125 |     |     |     |
| 40 | Lys | Pro | Lys | Asp | Thr | Leu | Met | Ile | Ser | Arg | Thr | Pro | Glu | Val | Thr | Cys |
|    | 130 |     |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |
| 45 | Val | Val | Val | Asp | Val | Ser | His | Glu | Asp | Pro | Glu | Val | Lys | Phe | Asn | Trp |
|    | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

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|    |                    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|----|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|    | Tyr                | Val | Asp | Gly | Val | Glu | Val | His | Asn | Ala | Lys | Thr | Lys | Pro | Arg | Glu |  |
|    |                    |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| 5  | Glu                | Gln | Tyr | Asn | Ser | Thr | Tyr | Arg | Val | Val | Ser | Val | Leu | Thr | Val | Leu |  |
|    |                    |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |  |
| 10 | His                | Gln | Asp | Trp | Leu | Asn | Gly | Lys | Glu | Tyr | Lys | Cys | Lys | Val | Ser | Asn |  |
|    |                    |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |  |
| 15 | Lys                | Ala | Leu | Pro | Ala | Pro | Ile | Glu | Lys | Thr | Ile | Ser | Lys | Ala | Lys | Gly |  |
|    |                    | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |  |
| 20 | Gln                | Pro | Arg | Glu | Pro | Gln | Val | Tyr | Thr | Leu | Pro | Pro | Ser | Arg | Glu | Glu |  |
|    | 225                |     |     |     |     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |  |
| 25 | Met                | Thr | Lys | Asn | Gln | Val | Ser | Leu | Thr | Cys | Leu | Val | Lys | Gly | Phe | Tyr |  |
|    |                    |     |     | 245 |     |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
| 30 | Pro                | Ser | Asp | Ile | Ala | Val | Glu | Trp | Glu | Ser | Asn | Gly | Gln | Pro | Glu | Asn |  |
|    |                    |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |  |
| 35 | Asn                | Tyr | Lys | Thr | Thr | Pro | Pro | Val | Leu | Asp | Ser | Asp | Gly | Ser | Phe | Phe |  |
|    |                    |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |  |
| 40 | Leu                | Tyr | Ser | Lys | Leu | Thr | Val | Asp | Lys | Ser | Arg | Trp | Gln | Gln | Gly | Asn |  |
|    |                    | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |  |
| 45 | Val                | Phe | Ser | Cys | Ser | Val | Met | His | Glu | Ala | Leu | His | Asn | His | Tyr | Thr |  |
|    | 305                |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |  |
| 50 | Gln                | Lys | Ser | Leu | Ser | Leu | Ser | Pro | Gly | Lys |     |     |     |     |     |     |  |
|    |                    |     |     | 325 |     |     |     |     |     | 330 |     |     |     |     |     |     |  |
| 55 | <210> 265          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <211> 106          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <212> PRT          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <213> Homo sapiens |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|    | <400> 265          |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
| 60 | Thr                | Val | Ala | Ala | Pro | Ser | Val | Phe | Ile | Phe | Pro | Pro | Ser | Asp | Glu | Gln |  |
|    | 1                  |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |  |
| 65 | Leu                | Lys | Ser | Gly | Thr | Ala | Ser | Val | Val | Cys | Leu | Leu | Asn | Asn | Phe | Tyr |  |
|    |                    |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |  |
| 70 | Pro                | Arg | Glu | Ala | Lys | Val | Gln | Trp | Lys | Val | Asp | Asn | Ala | Leu | Gln | Ser |  |
|    |                    |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |  |

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Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr  
 50 55 60

5 Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys  
 65 70 75 80

10 His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro  
 85 90 95

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  
 100 105

15 <210> 266  
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20 <400> 266

25 Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn  
 1 5 10 15

Arg Gln Phe Met Ala Glu Thr Gln Phe Thr Ser Gly Glu Lys Glu Gln  
 20 25 30

30 Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln  
 35 40 45

35 Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser  
 50 55 60

40 <210> 267  
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<400> 267

45 Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu  
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50 <210> 268  
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55 Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp  
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<210> 269

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5 <400> 269

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10

Ala Ser

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15

<400> 270

20

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 1 5 10 15

25

Lys Gly Lys Leu Asp Asp Tyr Gln Glu  
 20 25

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40

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Met Asn Thr Gln Gln Val Asn  
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50

<210> 273  
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55

<400> 273

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Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly  
1 5 10 15

5 Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln  
20 25 30

10 Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser  
35 40 45

Glu Val Glu Ser Thr Glu Tyr Val Asn Arg  
50 55

15 <210> 274  
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20 <400> 274

Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg  
1 5 10 15

25 <210> 275  
<211> 11  
<212> PRT  
<213> Homo sapiens

30 <400> 275

Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg  
1 5 10

35

## Claims

- 40 1. A pharmaceutical composition for use in a method of treatment of pancreatic cancer, comprising, as an active ingredient, an antibody or a fragment thereof which specifically has immunological reactivity with a CAPRIN-1 protein or a fragment thereof comprising 7 to 12 or more consecutive amino acid residues.
- 45 2. The pharmaceutical composition for use according to claim 1, wherein the CAPRIN-1 protein has an amino acid sequence represented by any of even-numbered SEQ ID NOs: 2 to 30, or an amino acid sequence having 80% or higher sequence identity to the amino acid sequence.
- 50 3. The pharmaceutical composition for use according to claim 1 or 2, wherein the pharmaceutical composition comprises, as an active ingredient, an antibody or a fragment thereof which has immunological reactivity with the fragment of the CAPRIN-1 protein, the fragment being a polypeptide consisting of 7 or more consecutive amino acid residues in a region of amino acid residue numbers 50 to 98, a region of amino acid residue numbers 233 to 343, or a region of amino acid residue number 527 to the C terminus, of an amino acid sequence represented by any of even-numbered SEQ ID NOs: 2 to 30 except for SEQ ID NOs: 6 and 18, or a polypeptide comprising the polypeptide as a partial sequence.
- 55 4. The pharmaceutical composition for use according to any one of claims 1 to 3, wherein the antibody or the fragment thereof is an antibody or a fragment thereof which has immunological reactivity with a partial CAPRIN-1 polypeptide having an amino acid sequence represented by SEQ ID NO: 273, 266, 270, 272, or 269, or an amino acid sequence

having 80% or higher sequence identity to the amino acid sequence, or a fragment thereof comprising 7 to 12 or more consecutive amino acid residues.

5 5. The pharmaceutical composition for use according to any one of claims 1 to 4, wherein the antibody is a monoclonal antibody or a polyclonal antibody.

6. The pharmaceutical composition for use according to any one of claims 1 to 5, wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, a single-chain antibody, or a multispecific antibody.

10 7. The pharmaceutical composition for use according to any one of claims 1 to 6, wherein the antibody or the fragment thereof is any of the following (a) to (y):

(a) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity determining regions (CDRs) of SEQ ID NOs: 37, 38, and 39 and a light chain variable region comprising CDRs of SEQ ID NOs: 41, 42, and 43 and has immunological reactivity with the CAPRIN-1 protein;

(b) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 47, 48, and 49 and a light chain variable region comprising CDRs of SEQ ID NOs: 51, 52, and 53 and has immunological reactivity with the CAPRIN-1 protein;

(c) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 57, 58, and 59 and a light chain variable region comprising CDRs of SEQ ID NOs: 61, 62, and 63 and has immunological reactivity with the CAPRIN-1 protein;

(d) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 67, 68, and 69 and a light chain variable region comprising CDRs of SEQ ID NOs: 71, 72, and 73 and has immunological reactivity with the CAPRIN-1 protein;

(e) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 77, 78, and 79 and a light chain variable region comprising CDRs of SEQ ID NOs: 81, 82, and 83 and has immunological reactivity with the CAPRIN-1 protein;

(f) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 87, 88, and 89 and a light chain variable region comprising CDRs of SEQ ID NOs: 91, 92, and 93 and has immunological reactivity with the CAPRIN-1 protein;

(g) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 97, 98, and 99 and a light chain variable region comprising CDRs of SEQ ID NOs: 101, 102, and 103 and has immunological reactivity with the CAPRIN-1 protein;

(h) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 107, 108, and 109 and a light chain variable region comprising CDRs of SEQ ID NOs: 111, 112, and 113 and has immunological reactivity with the CAPRIN-1 protein;

(i) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 117, 118, and 119 and a light chain variable region comprising CDRs of SEQ ID NOs: 121, 122, and 123 and has immunological reactivity with the CAPRIN-1 protein;

(j) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 127, 128, and 129 and a light chain variable region comprising CDRs of SEQ ID NOs: 121, 122, and 123 and has immunological reactivity with the CAPRIN-1 protein;

(k) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 132, 133, and 134 and a light chain variable region comprising CDRs of SEQ ID NOs: 136, 137, and 138 and has immunological reactivity with the CAPRIN-1 protein;

(l) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 142, 143, and 144 and a light chain variable region comprising CDRs of SEQ ID NOs: 146, 147, and 148 and has immunological reactivity with the CAPRIN-1 protein;

(m) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 142, 143, and 144 and a light chain variable region comprising CDRs of SEQ ID NOs: 152, 153, and 154 and has immunological reactivity with the CAPRIN-1 protein;

(n) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 157, 158, and 159 and a light chain variable region comprising CDRs of SEQ ID NOs: 161, 162, and 163 and has immunological reactivity with the CAPRIN-1 protein;

(o) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 171, 172, and 173 and has immunological reactivity with the CAPRIN-1 protein;

(p) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ

ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 177, 178, and 179 and has immunological reactivity with the CAPRIN-1 protein;

(q) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 182, 183, and 184 and has immunological reactivity with the CAPRIN-1 protein;

(r) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 187, 188, and 189 and has immunological reactivity with the CAPRIN-1 protein;

(s) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 167, 168, and 169 and a light chain variable region comprising CDRs of SEQ ID NOs: 192, 193, and 194 and has immunological reactivity with the CAPRIN-1 protein;

(t) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 197, 198, and 199 and a light chain variable region comprising CDRs of SEQ ID NOs: 201, 202, and 203 and has immunological reactivity with the CAPRIN-1 protein;

(u) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 207, 208, and 209 and a light chain variable region comprising CDRs of SEQ ID NOs: 211, 212, and 213 and has immunological reactivity with the CAPRIN-1 protein;

(v) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 217, 218, and 219 and a light chain variable region comprising CDRs of SEQ ID NOs: 221, 222, and 223 and has immunological reactivity with the CAPRIN-1 protein;

(w) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 227, 228, and 229 and a light chain variable region comprising CDRs of SEQ ID NOs: 231, 232, and 233 and has immunological reactivity with the CAPRIN-1 protein;

(x) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 237, 238, and 239 and a light chain variable region comprising CDRs of SEQ ID NOs: 241, 242, and 243 and has immunological reactivity with the CAPRIN-1 protein; and

(y) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs of SEQ ID NOs: 247, 248, and 249 and a light chain variable region comprising CDRs of SEQ ID NOs: 251, 252, and 253 and has immunological reactivity with the CAPRIN-1 protein.

8. The pharmaceutical composition for use according to any one of claims 1 to 7, wherein the antibody or the fragment thereof is conjugated with an antitumor agent.

9. The pharmaceutical composition for use according to any one of claims 1 to 7, which is for use by administration of the antibody or the fragment thereof in combination with an antitumor agent.

10. A pharmaceutical combination for use in a method of treatment of pancreatic cancer, comprising the pharmaceutical composition according to any one of claims 1 to 8 and a pharmaceutical composition comprising an antitumor agent.

## Patentansprüche

1. Pharmazeutische Zusammensetzung zur Verwendung in einem Verfahren zur Behandlung von Bauchspeicheldrüsensarkom, die als aktiven Bestandteil einen Antikörper oder ein Fragment davon umfasst, der/das spezifisch immunologische Reaktivität mit einem CAPRIN-1-Protein oder einem Fragment davon, das 7 bis 12 oder mehr aufeinanderfolgende Aminosäurereste umfasst, aufweist.

2. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 1, worin das CAPRIN-1-Protein eine durch eine der Seq.-ID Nr. 2 bis 30 mit gerader Nummer dargestellte Aminosäuresequenz oder eine Aminosäuresequenz mit 80 % oder mehr Sequenzidentität mit der Aminosäuresequenz aufweist.

3. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 1 oder 2, worin die pharmazeutische Zusammensetzung als aktiven Bestandteil einen Antikörper oder ein Fragment davon mit immunologischer Reaktivität mit dem Fragment des CAPRIN-1-Proteins umfasst, wobei das Fragment ein aus 7 oder mehr aufeinanderfolgenden Aminosäureresten in einer Region der Aminosäurerestenummern 50 bis 98, einer Region der Aminosäurerestenummern 233 bis 343 oder einer Region der Aminosäurerestenummer 527 bis zum C-Terminus einer durch eine der Seq.-ID Nr. 2 bis 30 mit gerader Nummer mit Ausnahme der Seq.-ID Nr. 6 und 18 dargestellten Aminosäuresequenz bestehendes Polypeptid oder ein das Polypeptid als Teilsequenz umfassendes Polypeptid ist.

4. Pharmazeutische Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 3, worin der Antikörper oder das Fragment davon ein Antikörper oder Fragment davon mit immunologischer Reaktivität mit einem partiellen CAPRIN-1-Polypeptid mit einer durch die Seq.-ID Nr. 273, 266, 270, 272 oder 269 dargestellten Aminosäuresequenz oder einer Aminosäuresequenz mit 80 % oder mehr Sequenzidentität mit der Aminosäuresequenz oder ein Fragment davon, das 7 bis 12 oder mehr aufeinanderfolgende Aminosäurereste umfasst, ist.

5. Pharmazeutische Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 4, worin der Antikörper ein monoklonaler Antikörper oder ein polyklonaler Antikörper ist.

6. Pharmazeutische Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 5, worin der Antikörper ein menschlicher Antikörper, ein humanisierter Antikörper, ein chimärer Antikörper, ein einkettiger Antikörper oder ein multispezifischer Antikörper ist.

7. Pharmazeutische Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 6, worin der Antikörper oder das Fragment davon einer bzw. eines der folgenden (a) bis (y) ist:

(a) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die komplementaritätsbestimmende Regionen (CDR) der Seq.-ID Nr. 37, 38 und 39 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 41, 42 und 43 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(b) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 47, 48 und 49 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 51, 52 und 53 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(c) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 57, 58 und 59 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 61, 62 und 63 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(d) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 67, 68 und 69 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 71, 72 und 73 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(e) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 77, 78 und 79 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 81, 82 und 83 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(f) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 87, 88 und 89 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 91, 92 und 93 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(g) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 97, 98 und 99 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 101, 102 und 103 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(h) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 107, 108 und 109 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 111, 112 und 113 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(i) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 117, 118 und 119 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 121, 122 und 123 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(j) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 127, 128 und 129 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 121, 122 und 123 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(k) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 132, 133 und 134 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 136, 137 und 138 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(l) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 142, 143 und 144 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 146, 147 und 148 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(m) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 142, 143 und 144 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 152, 153 und 154 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(n) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerekettenregion, die CDR der Seq.-ID Nr. 157, 158 und 159 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 161, 162

und 163 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(o) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 167, 168 und 169 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 171, 172 und 173 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(p) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 167, 168 und 169 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 177, 178 und 179 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(q) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 167, 168 und 169 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 182, 183 und 184 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(r) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 167, 168 und 169 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 187, 188 und 189 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(s) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 167, 168 und 169 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 192, 193 und 194 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(t) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 197, 198 und 199 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 201, 202 und 203 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(u) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 207, 208 und 209 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 211, 212 und 213 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(v) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 217, 218 und 219 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 221, 222 und 223 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(w) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 227, 228 und 229 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 231, 232 und 233 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist;

(x) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 237, 238 und 239 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 241, 242 und 243 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist; und

(y) ein Antikörper oder Fragment davon, der bzw. das eine variable Schwerkettenregion, die CDR der Seq.-ID Nr. 247, 248 und 249 umfasst, und eine variable Leichtkettenregion umfasst, die CDR der Seq.-ID Nr. 251, 252 und 253 umfasst, und immunologische Reaktivität mit dem CAPRIN-1-Protein aufweist.

8. Pharmazeutische Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 7, worin der Antikörper oder das Fragment davon mit einem Antitumormittel konjugiert ist.

9. Pharmazeutische Zusammensetzung zur Verwendung nach einem der Ansprüche 1 bis 7, die der Verwendung durch Verabreichung des Antikörpers oder des Fragments davon in Kombination mit einem Antitumormittel dient.

10. Pharmazeutische Kombination zur Verwendung in einem Verfahren zur Behandlung von Bauchspeicheldrüsenkrebs, die eine pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 8 und eine pharmazeutische Zusammensetzung umfasst, die ein Antitumormittel umfasst.

## Revendications

1. Composition pharmaceutique pour utilisation dans un procédé de traitement du cancer du pancréas, comprenant, en tant que substance active, un anticorps ou un fragment de celui-ci qui présente spécifiquement une réactivité immunologique avec une protéine CAPRINE-1 ou un fragment de celle-ci comprenant de 7 à 12 résidus d'acides aminés consécutifs ou davantage.

2. Composition pharmaceutique pour utilisation selon la revendication 1, dans laquelle la protéine CAPRINE-1 comporte une séquence d'acides aminés représentée par l'une quelconque des SEQ ID N° : 2 à 30 de numéro pair ou une séquence d'acides aminés présentant une identité de séquence supérieure ou égale à 80 % avec la séquence d'acides aminés.

3. Composition pharmaceutique pour utilisation selon la revendication 1 ou 2, laquelle composition pharmaceutique comprend, en tant que substance active, un anticorps ou un fragment de celui-ci qui présente une réactivité immunologique avec le fragment de la protéine CAPRINE-1, le fragment étant un polypeptide constitué de 7 résidus d'acides aminés consécutifs ou davantage dans une région des numéros de résidus d'acides aminés 50 à 98, une région des numéros de résidus d'acides aminés 233 à 343, ou une région du numéro de résidu d'acide aminé 527 à la terminaison C, d'une séquence d'acides aminés représentée par l'une quelconque des SEQ ID N° : 2 à 30 de numéro pair à l'exception des SEQ ID N° : 6 et 18, ou un polypeptide comprenant le polypeptide en tant que séquence partielle.
4. Composition pharmaceutique pour utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle l'anticorps ou le fragment de celui-ci est un anticorps ou un fragment de celui-ci qui présente une réactivité immunologique avec un polypeptide de CAPRINE-1 partiel comportant une séquence d'acides aminés représentée par SEQ ID N° : 273, 266, 270, 272 ou 269 ou une séquence d'acides aminés présentant une identité de séquence supérieure ou égale à 80 % avec la séquence d'acides aminés, ou un fragment de celui-ci comprenant de 7 à 12 résidus d'acides aminés consécutifs ou davantage.
5. Composition pharmaceutique pour utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle l'anticorps est un anticorps monoclonal ou un anticorps polyclonal.
6. Composition pharmaceutique pour utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle l'anticorps est un anticorps humain, un anticorps humanisé, un anticorps chimérique, un anticorps à une seule chaîne ou un anticorps multispécifique.
7. Composition pharmaceutique pour utilisation selon l'une quelconque des revendications 1 à 6, dans laquelle l'anticorps ou le fragment de celui-ci est l'un quelconque des éléments (a) à (y) suivants :
  - (a) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des régions déterminant la complémentarité (CDR) de SEQ ID N° : 37, 38 et 39 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 41, 42 et 43 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (b) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 47, 48 et 49 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 51, 52 et 53 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (c) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 57, 58 et 59 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 61, 62 et 63 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (d) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 67, 68 et 69 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 71, 72 et 73 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (e) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 77, 78 et 79 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 81, 82 et 83 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (f) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 87, 88 et 89 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 91, 92 et 93 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (g) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 97, 98 et 99 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 101, 102 et 103 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (h) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 107, 108 et 109 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 111, 112 et 113 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (i) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 117, 118 et 119 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 121, 122 et 123 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (j) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 127, 128 et 129 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 121, 122 et 123 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;
  - (k) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant

des CDR de SEQ ID N° : 132, 133 et 134 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 136, 137 et 138 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(l) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 142, 143 et 144 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 146, 147 et 148 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(m) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 142, 143 et 144 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 152, 153 et 154 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(n) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 157, 158 et 159 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 161, 162 et 163 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(o) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 167, 168 et 169 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 171, 172 et 173 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(p) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 167, 168 et 169 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 177, 178 et 179 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(q) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 167, 168 et 169 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 182, 183 et 184 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(r) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 167, 168 et 169 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 187, 188 et 189 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(s) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 167, 168 et 169 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 192, 193 et 194 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(t) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 197, 198 et 199 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 201, 202 et 203 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(u) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 207, 208 et 209 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 211, 212 et 213 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(v) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 217, 218 et 219 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 221, 222 et 223 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(w) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 227, 228 et 229 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 231, 232 et 233 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ;

(x) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 237, 238 et 239 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 241, 242 et 243 et qui présente une réactivité immunologique avec la protéine CAPRINE-1 ; et

(y) un anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDR de SEQ ID N° : 247, 248 et 249 et une région variable de chaîne légère comprenant des CDR de SEQ ID N° : 251, 252 et 253 et qui présente une réactivité immunologique avec la protéine CAPRINE-1.

8. Composition pharmaceutique pour utilisation selon l'une quelconque des revendications 1 à 7, dans laquelle l'anticorps ou le fragment de celui-ci est conjugué à un agent antitumoral.

9. Composition pharmaceutique pour utilisation selon l'une quelconque des revendications 1 à 7, qui est destinée à une utilisation par administration de l'anticorps ou du fragment de celui-ci en association avec un agent antitumoral.

10. Combinaison pharmaceutique pour utilisation dans un procédé de traitement du cancer du pancréas, comprenant la composition pharmaceutique selon l'une quelconque des revendications 1 à 8 et une composition pharmaceutique comprenant un agent antitumoral.

## REFERENCES CITED IN THE DESCRIPTION

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## GYÓGYÁSZATI KÉSZÍTMÉNY HASNYÁLMIRIGYRÁK KEZELÉSÉRE ÉS/VAGY MEGELŐZÉSÉRE

### Szabadalmi igénypontok

1. Gyógyászati készítmény hasnyálmirigyrák kezelési eljárásában történő alkalmazásra, amely készítmény hatóanyagként tartalmaz olyan antitestet vagy annak fragmensét, amely specifikus immunológiai reaktivitással rendelkezik egy CAPRIN-1 fehérjével vagy annak olyan fragmensével, amely 7-12 vagy több egymást követő aminosavat tartalmaz.
2. A gyógyászati készítmény alkalmazásra az 1. igénypont szerint, ahol a CAPRIN-1 fehérje rendelkezik a SEQ ID NO: 2-30 szerinti (azaz a 2-30. azonosítási számú szekvenciák) közül a páros azonosítási számúak bármelyikének megfelelő aminosav-szekvenciával, vagy olyan aminosav-szekvenciával, amely legalább 80%-os szekvenciaazonosságot mutat az aminosav-szekvenciával.
3. A gyógyászati készítmény alkalmazásra az 1. vagy 2. igénypont szerint, ahol a gyógyászati készítmény hatóanyagként tartalmaz olyan antitestet vagy annak fragmensét, amely immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjének a fragmensével, a fragmens olyan polipeptid, amely 7 vagy több egymást követő aminosav-maradékból áll a SEQ ID NO: 6 és 18 kivételével a SEQ ID NO: 2-30 szerinti (azaz a 2-30. azonosítási számú) közül a páros azonosítási számúak bármelyikének megfelelő aminosav-szekvencia 50-98. aminosavai által alkotott régióból, a 233-343. aminosavai által alkotott régióból vagy az 527. aminosavától a C-terminálisig tartó régióból, vagy olyan polipeptid, amely szekvencia-részletként tartalmazza a polipeptidet.
4. A gyógyászati készítmény alkalmazásra az 1-3. igénypontok bármelyike szerint, ahol az antitest vagy a fragmense olyan antitest vagy fragmense,

amely immunológiai reaktivitással rendelkezik egy részleges CAPRIN-1 polipeptiddel, amely rendelkezik a SEQ ID NO: 273, 266, 270, 272 vagy 269 által bemutatott aminosav-szekvenciával vagy olyan aminosav-szekvenciával, amely legalább 80%-os szekvenciaazonosságot mutat az aminosav-szekvenciával, vagy annak egy 7-12 vagy több egymást követő aminosavat tartalmazó fragmensével.

5. A gyógyászati készítmény alkalmazásra az 1-4. igénypontok bármelyike szerint, ahol az antitest monoklonális antitest vagy poliklonális antitest.
6. A gyógyászati készítmény alkalmazásra az 1-5. igénypontok bármelyike szerint, ahol az antitest humán antitest, humanizált antitest, kiméra antitest, egyláncú antitest vagy multispecifikus antitest.
7. A gyógyászati készítmény alkalmazásra az 1-6. igénypontok bármelyike szerint, ahol az antitest vagy a fragmense a következő (a)-(y) pontok bármelyike szerinti:

(a) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 37, 38 és 39 szerinti komplementaritás-meghatározó régiókat (CDR-eket), és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 41, 42 és 43 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(b) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 47, 48 és 49 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 51, 52 és 53 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(c) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 57, 58 és 59 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 61, 62 és 63 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(d) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 67, 68 és 69 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 71, 72 és 73 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(e) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 77, 78 és 79 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 81, 82 és 83 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(f) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 87, 88 és 89 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 91, 92 és 93 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(g) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 97, 98 és 99 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 101, 102 és 103 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(h) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 107, 108 és 109 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 111, 112 és 113 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(i) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 117, 118 és 119 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 121, 122 és 123 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(j) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 127, 128 és 129 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 121,

122 és 123 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(k) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 132, 133 és 134 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 136, 137 és 138 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(l) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 142, 143 és 144 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 146, 147 és 148 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(m) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 142, 143 és 144 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 152, 153 és 154 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(n) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 157, 158 és 159 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 161, 162 és 163 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(o) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 167, 168 és 169 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 171, 172 és 173 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(p) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 167, 168 és 169 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 177, 178 és 179 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(q) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 167, 168 és 169 szerinti CDR-eket,

és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 182, 183 és 184 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(r) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 167, 168 és 169 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 187, 188 és 189 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(s) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 167, 168 és 169 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 192, 193 és 194 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(t) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 197, 198 és 199 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 201, 202 és 203 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(u) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 207, 208 és 209 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 211, 212 és 213 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(v) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 217, 218 és 219 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 221, 222 és 223 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(w) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 227, 228 és 229 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 231, 232 és 233 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével;

(x) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 237, 238 és 239 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 241, 242 és 243 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével; és

(y) antitest vagy fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 247, 248 és 249 szerinti CDR-eket, és olyan könnyűlánc variábilis régiót, amely tartalmaz a SEQ ID NO: 251, 252 és 253 szerinti CDR-eket, és immunológiai reaktivitással rendelkezik a CAPRIN-1 fehérjével.

8. A gyógyászati készítmény alkalmazásra az 1-7. igénypontok bármelyike szerint, ahol az antitest vagy a fragmense tumorelles ágenshez van konjugálva.
9. A gyógyászati készítmény alkalmazásra az 1-7. igénypontok bármelyike szerint, amely olyan alkalmazásra szolgál, amelynek során beadjuk az antitestet vagy a fragmensét tumorelles ágenssel kombináltan.
10. Gyógyászati kombináció hasnyálmirigyrák kezelési eljárásában történő alkalmazásra, amely kombináció tartalmaz az 1-8. igénypontok bármelyike szerinti gyógyászati készítményt, valamint tumorelles ágenszt tartalmazó gyógyászati készítményt.