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(54) **Immunitásindukáló ágens és eljárás rák detektálására**

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(54) **IMMUNITY-INDUCING AGENT AND METHOD FOR DETECTION OF CANCER**

IMMUNITÄTSINDUZIERENDES MITTEL UND VERFAHREN FÜR DEN NACHWEIS VON KREBS

AGENT INDUISANT UNE IMMUNITÉ ET PROCÉDÉ DE DÉTECTION D'UN CANCER

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- **NOBUTAKA KIYOKAWA ET AL.: 'B-zenku Saibosei Lymphoblastic Lymphoma no Shindan Marker Toshite no CD179a/b no Yuyosei' NIPPON BYORI GAKKAI KAISHI vol. 93, no. 1, 2004, page 413, XP008140614**
- **KIYOKAWA, N. ET AL.: 'Diagnostic importance of CD179a/b as markers of precursor B-cell lymphoblastic lymphoma' MOD PATHOL vol. 17, no. 4, 2004, pages 423 - 429, XP008140586**

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Description

TECHNICAL FIELD

[0001] The present invention relates to a novel immunity-inducing agent useful as a therapeutic and/or prophylactic agent for cancer. Further, the present invention relates to a novel method for detection of cancer.

BACKGROUND ART

[0002] Cancer is the commonest cause for death among all of the causes for death, and therapies carried out therefor at present are mainly surgical treatment in combination with radiotherapy and chemotherapy. In spite of the developments of new surgical methods and discovery of new anti-cancer agents in recent years, treatment results of cancers are not improved very much at present except for some cancers. In recent years, by virtue of the development in molecular biology and cancer immunology, cancer antigens recognized by cytotoxic T cells reactive with cancers, as well as the genes encoding the cancer antigens, were identified, and expectations for antigen-specific immunotherapies have been raised (Non-patent Literature 1).

[0003] In immunotherapy, to reduce side effects, it is necessary that the peptide, polypeptide or protein recognized as the antigen exist hardly in normal cells and exist specifically in cancer cells. In 1991, Boon et al. of Ludwig Institute in Belgium isolated a human melanoma antigen MAGE 1, which is recognized by CD8-positive T cells, by a cDNA-expression cloning method using an autologous cancer cell line and cancer-reactive T cells (Non-patent Literature 2). Thereafter, the SEREX (serological identifications of antigens by recombinant expression cloning) method, wherein tumor antigens recognized by antibodies produced in the living body of a cancer patient in response to the cancer of the patient himself are identified by application of a gene expression cloning method, was reported (Non-patent Literature 3; Patent Literature 1), and several cancer antigens have been isolated by this method (Non-patent Literatures 4 to 9). Using a part thereof as targets, clinical tests for cancer immunotherapy have started.

[0004] On the other hand, as in human, a number of tumors such as mammary gland cancer, leukemia and lymphoma are known in dogs and cats, and they rank high also in the statistics of diseases in dogs and cats. However, at present, no therapeutic agent and prophylactic agent exist which are effective for cancers in dogs and cats. Most of tumors in dogs and cats are realized by owners only after they advanced to grow bigger, and in many cases, it is already too late to visit a hospital to receive surgical excision of the tumor or administration of a human drug (an anticancer preparation or the like), so that those dogs and cats often die shortly after the treatment. Under such circumstances, if therapeutic agents and prophylactic agents for cancer effective for dogs and cats become available, their uses for canine cancers are expected to be developed.

[0005] Since early detection of cancer leads to good treatment results, a method for detecting cancer which can be easily carried out by testing serum, urine or the like without physical and economical burden to cancer patients is demanded. Recently, methods wherein tumor products such as tumor markers are measured have been widely used as diagnostic methods using blood or urine. Examples of the tumor products include tumor-related antigens, enzymes, specific proteins, metabolites, tumor genes, products of tumor genes, and tumor-suppressor genes, and, in some cancers, a carcinoembryonic antigen CEA, glycoproteins CA19-9 and CA125, a prostate-specific antigen PSA, calcitonin which is a peptide hormone produced in thyroid, and the like are utilized as tumor markers in cancer diagnosis (Non-patent Literature 10). However, in most types of cancers, there are no tumor markers useful for cancer diagnosis. Further, since most of the tumor markers currently known exist only in very small amounts (e.g., in the order of pg/mL) in body fluid, their detection requires a highly sensitive measurement method or a special technique. Under such circumstances, if a novel cancer detection method by which various cancers can be detected by simple operations is provided, its use for diagnosis of various cancers are expected to be developed.

[0006] CD179b is known to be a part of the surrogate light chain of immunoglobulin and to be expressed on the membrane surfaces of precursor cells of B cells (pre-B cells and pro-B cells). It disappears upon differentiation of B cells and is not expressed in mature B cells. However, CD179b is known to be expressed in leukemia (pre-B cell leukemia) cells produced by cancerization of pre-B cells (Non-patent Literatures 10 and 11). Further, CD179b is known to be expressed also in lymphoma (pre-B cell lymphoma) cells produced by cancerization of pre-B cells, and able to be used as a diagnostic marker for pre-B cell lymphoma (Non-patent Literature 12). However, its specific expression has not been reported for leukemia cells other than pre-B cell leukemia cells, lymphomas other than pre-B cell lymphoma, breast cancer cells and the like. Further, there has been no report suggesting that enhancement of immunity against CD179b is useful for therapy and/or prophylaxis of cancer. An anti-CD44 antibody that has homology to CD1179b and use of the antibody to treat or diagnose CD44-expressing cancer cells is disclosed in Patent Literature 2. A polypeptide having homology to CD179b is reported to be upregulated in liposarcoma, synovial sarcoma and soft tissue sarcoma in Patent Literature 3.

PRIOR ART LITERATURES

Patent Literature

[0007]

Patent Literature 1: US 5698396 B
Patent Literature 2: WO 2004/024750
Patent Literature 3: WO 2004/048938

Non-patent Literatures

[0008]

Non-patent Literature 1: Tsuyoshi Akiyoshi, "Cancer and Chemotherapy", 1997, Vol. 24, pp. 551-519
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)
Non-patent Literature 10: Adv. Immunol., 63:1-41 (1996)
Non-patent Literature 11: Blood, 92:4317-4324 (1998)
Non-patent Literature 12: Modem Pathology, 17:423-429 (2004)

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0009] The present invention aims to discover a novel polypeptide useful as an agent for therapy and/or prophylaxis and/or the like of cancer, thereby providing use of the polypeptide for an immunity-inducing agent. The present invention also aims to provide a method for detection of cancer, which is useful for diagnosis of cancer.

MEANS FOR SOLVING THE PROBLEMS

[0010] The present inventors intensively studied to obtain, by the SEREX method using serum from a canine patient from which a canine breast cancer tissue-derived cDNA library was prepared, cDNA encoding a protein which binds to antibodies existing in the serum derived from the tumor-bearing living body, and, based on a the cDNA, canine CD179b polypeptides having the amino acid sequences shown in the odd number IDs of SEQ ID NOs:5 to 95 (that is, SEQ ID NOs:5, 7, 9, 11, 13, 15, ..., 91 and 93) in SEQUENCE LISTING were prepared. Further, based on a human homologous gene of the obtained genes, a human CD 179b polypeptide having the amino acid sequence shown in SEQ ID NO:3 was prepared, and, similarly, based on a bovine homologous gene, a bovine CD179b polypeptide having the amino acid sequence shown in SEQ ID NO:95 was prepared. The present inventors then discovered that that these CD179b polypeptides are specifically expressed in breast cancer, leukemia and lymphoma cells. Further, the present inventors discovered that, by administration of these CD179b to a living body, immunocytes against CD179b can be induced in the living body, and a tumor in the living body expressing CD179b can be regressed. Further, the present inventors discovered that a recombinant vector comprising a polynucleotide encoding a CD179b polypeptide or a fragment thereof such that it can be expressed induces an anti-tumor effect against cancer expressing CD179b in the living body.

[0011] Further, the present inventors discovered that a partial polypeptide in a CD179b protein has a capacity to be presented by antigen-presenting cells, thereby allowing activation and growth of cytotoxic T cells specific to the peptide (immunity-inducing activity), and therefore that the peptide is useful for therapy and/or prophylaxis of cancer, and, further, that antigen-presenting cells contacted with the peptide and T cells contacted with the antigen-presenting cells are useful for the therapy and/or prophylaxis of cancer. Further, the present inventors discovered that, since a recombinant polypeptide prepared based on the amino acid sequence of the above CD179b protein specifically reacts only with serum of a tumor-bearing living body, cancer can be detected therewith. Based on the above discoveries, the present inventors completed the present invention.

[0012] Thus, the present invention provides:

- agents, isolated antigen-presenting cells and isolated T cells for use in a method for therapy and/or prophylaxis of breast cancer and/or leukemia;
- methods for detecting breast cancer and/or leukemia;
- reagents for use in an in vivo method for detecting a breast cancer and/or leukemia; and
- in vitro use of a reagent for detecting a breast cancer and/or leukemia,

all as defined in the claims.

EFFECT OF THE INVENTION

[0013] By the present invention, a novel immunity-inducing agent useful for therapy and/or prophylaxis and/or the like of breast cancer and/or leukemia is provided. As particularly described in later-mentioned Examples, by administering the polypeptide used in the present invention to a tumor-bearing animal, immunocytes can be induced in the body of the tumor-bearing animal, and a breast cancer and/or leukemia which has already occurred can be reduced or regressed.

[0014] Further, by the present invention, a novel method for detection of breast cancer and/or leukemia is provided. Since measurement of expression of the polypeptide in a sample by the method of the present invention enables detection of invisible small cancers and cancers which exist in deep parts of a body, the method is also useful for early detection of cancers in medical examinations and the like. If the method of the present invention is used in following-up of patients after cancer therapy, recurrence of the cancer can be detected in its early stage. Moreover, the method of the present invention makes it possible to assess the stage of cancer progression such as growth of the tumor, invasion of the tumor to the surrounding tissues, and metastasis of the cancer to lymph nodes and distant organs.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015]

Fig. 1 is a diagram showing the expression patterns of the gene encoding the CD179b protein in normal tissues and tumor cell lines. Reference numeral 1 represents the expression pattern of the gene encoding the CD179b protein; and reference numeral 2 represents the expression pattern of the GAPDH gene. In Fig. 1, reference numeral 1 in the ordinate represents the expression pattern of the gene identified as described above, and reference numeral 2 represents the expression pattern of the GAPDH gene as the control for comparison.

In Fig. 2, reference numerals 3, 4, 5, 6, 7, 8, 9 and 10 in the abscissa indicate the IFN-γ-producing abilities of HLA-A0201-positive CD8-positive T cells due to stimulation from T2 cells pulsed with the peptides of SEQ NOs:108, 109, 110, 113, 114, 115, 116 and 117, respectively. Reference numeral 11 indicates the result for the peptide of SEQ ID NO: 118 used as the negative control (peptide having a sequence outside the scope of the present invention).

In Fig. 3, reference numerals 12, 13, 14, 15, 16, 17, 18 and 19 in the abscissa indicate the cytotoxic activities of HLA-A0201-positive CD8-positive T cells against Namalwa cells, which cells were stimulated using SEQ ID NOs:108, 109, 110, 113, 114, 115, 116 and 117, respectively. Reference numeral 20 indicates the cytotoxic activity of CD8-positive T cells induced using the peptide of the negative control (SEQ ID NO: 118).

In Fig. 4, reference numerals 21, 22, 23, 24 and 25 in the abscissa indicate the IFN-γ-producing abilities of HLA-A24-positive CD8-positive T cells due to stimulation from JTK-LCL cells pulsed with the peptides of SEQ NOs:110, 111, 112, 115 and 116, respectively. Reference numeral 26 indicates the result for the peptide of SEQ ID NO:118 used as the negative control.

In Fig. 5, reference numerals 27, 28, 29, 30 and 31 indicate the cytotoxic activities of HLA-A24-positive CD8-positive T cells stimulated with the peptides of SEQ ID NO:110, 111, 112, 115 and 116, respectively, against JTK-LCL cells. Reference numeral 32 indicates the cytotoxic activity of CD8-positive T cells induced using the peptide of the negative control (SEQ ID NO:118).

BEST MODE FOR CARRYING OUT THE INVENTION

<Polypeptide>

[0016] Examples of the polypeptide contained in the immunity-inducing agent of the present invention as an effective ingredient include one or more polypeptide(s) selected from the polypeptides of (a), (b) and (c) below:

(a) a polypeptide consisting of amino acids in any one of the amino acid sequences shown in the odd number IPs

of SEQ ID NOs:3 to 95 (that is, SEQ ID NO:3, 5, 7, 9, 11, 13, 15,..., 93 and 95) and has an immunity-inducing activity;
(b) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110. SEQ ID NO: 111, SEQ ID NO:112, SEQ ID NO: 113. SEQ ID NO: 114. SEQ ID NO: 115, SEQ ID NO: 116 or SEQ ID NO: 117; and
c) a polypeptide comprising as a partial sequence thereof an amino acid sequence as shown in SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115. SEQ ID NO:116 or SEQ ID NO:117, said polypeptide having 8 to 12 amino acidresidues.

[0017] As used herein, the term "polypeptide" means a molecule formed by a plurality of amino acids linked together by peptide bonds, and includes not only polypeptide molecules having large numbers of amino acids constituting them, but also low-molecular-weight molecules having small numbers of amino acids (oligopeptides), and full-length molecules. In the present invention, proteins constituted by the total lengths of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 and 95 are also included therein.

[0018] As used herein, the term "having an amino acid sequence" means that amino acid residues are arrayed in a specific order. Therefore, for example, "a polypeptide having the amino acid sequence shown in SEQ ID NO:3" means a polypeptide having the amino acid sequence of Leu Leu Arg Pro ... (snip) ... Ala Glu Cys Ser shown in SEQ ID NO:3, which polypeptide has a size of 176 amino acid residues. Further, for example, "polypeptide having the amino acid sequence shown in SEQ ID NO:3" may also be abbreviated as "polypeptide of SEQ ID NO:3". This also applies to the term "having a base sequence".

[0019] As used herein, the term "immunity-inducing activity" means an ability to induce immunocytes which secrete cytokines such as interferon in a living body.

[0020] Whether or not a polypeptide has an immunity-inducing activity can be confirmed using, for example, the known ELISPOT assay. More particularly, for example, as described in the Examples below, cells such as peripheral blood mononuclear cells are obtained from a living body to which a polypeptide whose immunity-inducing activity is to be evaluated was administered, which cells are then cocultivated with the polypeptide, followed by measuring the amount(s) of a cytokine(s) and/or a chemokine(s) such as IFN-γ and/or interleukin (IL) produced by the cells using a specific antibody/antibodies, thereby measuring the number of immunocytes in the cells, which enables evaluation of the immunity-inducing activity.

[0021] Alternatively, as described in the later-mentioned Examples, when a recombinant polypeptide prepared based on the amino acid sequence of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 is administered to a tumor-bearing animal, the tumor can be reduced or regressed by its immunity-inducing activity. Thus, the above immunity-inducing activity can be evaluated also as an ability to suppress the growth of cancer cells expressing the polypeptide of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95, or to cause reduction or disappearance of a cancer tissue (tumor) (hereinafter referred to as "anti-tumor activity"). The anti-tumor activity of a polypeptide can be confirmed by, for example, observation of whether or not the tumor is reduced or regressed when the polypeptide was administered to a tumor-bearing living body, as more particularly described in the Examples below.

[0022] Alternatively, the anti-tumor activity of a polypeptide can be evaluated also by observation of whether or not T cells stimulated with the polypeptide (that is, T cells brought into contact with antigen-presenting cells presenting the polypeptide) show a cytotoxic activity against tumor cells in vitro. The contact between the T cells and the antigen-presenting cells can be carried out by cocultivation of the both in a liquid medium, as mentioned below. Measurement of the cytotoxic activity can be carried out by, for example, a known method called ^{51}Cr release assay described in Int. J. Cancer, 58: p317, 1994.

[0023] In cases where the polypeptide is used for therapy and/or prophylaxis of cancer, the evaluation of the immunity-inducing activity is preferably carried out using the anti-tumor activity as an index, although the index is not restricted.

[0024] The amino acid sequence shown in each of SEQ ID NOs:3, 5, 7, 9, 11, 13, 15, ... 93 and 95 in SEQUENCE LISTING is the amino acid sequence of a polypeptide which binds to an antibody specifically existing in serum derived from a tumor-bearing dog in the SEREX method using serum of the canine patient from which a canine mammary gland cancer-derived cDNA library was prepared, or the amino acid sequence of CD179b isolated as a human homologous factor (homologue) of the polypeptide (see Example 1 below). The polypeptide (a) is a polypeptide which consists any one of the amino acid sequences shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 and 95 in SEQUENCE LISTING and has an immunity-inducing activity. As known in the art, a polypeptide having not less than about 7 amino acid residues can exert its antigenicity and immunogenicity. Thus, a polypeptide having the amino acid sequence shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 can have an immunity-inducing activity, so that it can be used for preparation of the immunity-inducing agent of the present invention.

[0025] As a principle of immune induction by administration of a cancer antigenic polypeptide, the following process is known: the polypeptide is incorporated into an antigen-presenting cell and then degraded into smaller fragments by peptidases in the cell, followed by presentation of the fragments on the surface of the cell. The fragments are then recognized by a cytotoxic T cell or the like, which selectively kills cells presenting the antigen. The size of the polypeptide

presented on the surface of the antigen-presenting cell is relatively small and about 7 to 30 amino acids.

[0026] In some cases, these relatively small polypeptides are presented directly on the surface of the antigen-presenting cells without incorporation thereof into the antigen-presenting cells.

[0027] Further, since a polypeptide incorporated into an antigen-presenting cell is cleaved at random sites by peptidases in the cell to yield various polypeptide fragments, which are then presented on the surface of the antigen-presenting cell, administration of a large polypeptide such as the entire region of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 inevitably causes production of polypeptide fragments by degradation thereof in the antigen-presenting cell, which fragments are effective for immune induction via the antigen-presenting cell. Therefore, also for immune induction via antigen-presenting cells, a large polypeptide can be used, and the polypeptide may be composed of the entire region of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95.

[0028] Further, the polypeptides of the present invention can be checked with a checking medium by which epitope peptides having binding motifs of various types of HLA and composed of 8 to 12, preferably 9 to 10 amino acids can be searched, for example, HLA Peptide Binding Predictions (http://bimas.dcrt.nih.gov/molbio/hla_bind/index.html) in Bio-informatics & Molecular Analysis Selection (BIMAS), to screen peptides which may be epitope peptides. More particularly, a polypeptide composed of the amino acid sequence shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 is preferred, and, in the polypeptide of SEQ ID NO:3, the polypeptides shown in SEQ ID NOs:108 to 117 are more preferred.

[0029] The polypeptide (b) is the polypeptide consisting of the amino acid sequence shown in SEQ ID NO:100, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114. SEQ ID NO:115, SEQ It NO:116 or SEQ ID NO:117 and has an immunity-inducing activity.

[0030] The polypeptide (c) comprises the polypeptide (b) as a partial sequence thereof and has an immunity-inducing activity. That is, the polypeptide (c) has another/other amino acid(s) or polypeptide(s) added at one end or the both ends of the polypeptide (b), said polypeptide having to 12 amino acid residues and has an immunity-inducing activity. Such a polypeptide can also be used for preparation of the immunity-inducing agent of the present invention.

[0031] The above-described polypeptides can be synthesized by, for example, a chemical synthesis method such as the Fmoc method (fluorenylmethyloxycarbonyl method) or the tBoc method (t-butyloxycarbonyl method). Further, they can be synthesized by conventional methods using various types of commercially available peptide synthesizers. Further, the polypeptide of interest can be obtained using known genetic engineering techniques, by preparing a polynucleotide encoding the above polypeptide and incorporating the polynucleotide into an expression vector, which is then transfected into a host cell, followed by allowing the polypeptide to be produced in the host cell.

[0032] The polynucleotide encoding the above polypeptide can be easily prepared by a known genetic engineering technique or a conventional method using a commercially available nucleic acid synthesizer. For example, DNA having the base sequence shown in SEQ ID NO:4 can be prepared by carrying out PCR using a canine chromosomal DNA or cDNA library as a template, and a pair of primers designed such that the base sequence shown in SEQ ID NO:4 can be amplified therewith. In the case of DNA having the base sequence of SEQ ID NO: 1, this can be similarly prepared by using a human chromosomal DNA or cDNA library as the template. The reaction conditions for the PCR can be set appropriately, and examples thereof include, but are not limited to, repeating the reaction process of 94°C for 30 seconds (denaturation), 55°C for 30 seconds to 1 minute (annealing) and 72°C for 2 minutes (extension) for, for example, 30 cycles, followed by the reaction at 72°C for 7 minutes. Methods, conditions and the like of PCR are described in, for example, Ausubel et al., Short Protocols in Molecular Biology, 3rd ed., A compendium of Methods from Current Protocols in Molecular Biology (1995), John Wiley & Sons (in particular, Chapter 15). Further, the desired DNA can be isolated by preparing an appropriate probe(s) or primer(s) based on the information of the base sequences and the amino acid sequences shown in SEQ ID NO: to 95 in SEQUENCE LISTING in the present specification, and screening a cDNA library of human, dog, bovine or the like using the probe(s) or primer(s). The cDNA library is preferably prepared from a cell, organ or tissue expressing the protein of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95. The above-described operations such as preparation of the probe(s) or primer(s), construction of a cDNA library, screening of the cDNA library and cloning of the gene of interest are known to those skilled in the art, and can be carried out according to the methods described in, for example, Sambrook et al., Molecular Cloning, Second Edition, Current Protocols in Molecular Biology (1989); and Ausubel et al. (described above). From the thus obtained DNA, DNA encoding the polypeptide (a) can be obtained. Further, since codons encoding each amino acid are known, a base sequence of a polynucleotide encoding a specific amino acid sequence can be easily specified. Therefore, the base sequences of polynucleotides encoding the polypeptide (b) and polypeptide (c) can also be easily specified, so that such polynucleotides can also be easily synthesized using a commercially available nucleic acid synthesizer according to a conventional method.

[0033] The host cells are not restricted as long as they can express the above-described polypeptide, and examples thereof include, but are not limited to, prokaryotic cells such as *E. coli;* and eukaryotic cells such as mammalian cultured cells including monkey kidney cells COS 1, Chinese hamster ovary cells CHO, a human embryonic kidney cell line HEK293 and a mouse embryonic skin cell line NIH3T3; budding yeast; fission yeast; silkworm cells; and *Xenopus laevis* egg cells.

[0034] In cases where prokaryotic cells are used as the host cells, an expression vector having the origin that enables

its replication in a prokaryotic cell, promoter, ribosome binding site, multicloning site, terminator, drug resistant gene, nutrient complementary gene and/or the like is used. Examples of the expression vector for *E. coli* include the pUC system, pBluescriptII, pET expression system and pGEX expression system. By incorporating a DNA encoding the above polypeptide into such an expression vector and transforming prokaryotic host cells with the vector, followed by culturing the resulting transformants, the polypeptide encoded by the DNA can be expressed in the prokaryotic host cells. In this process, the polypeptide can also be expressed as a fusion protein with another protein (e.g., green fluorescent protein (GFP) or glutathione S-transferase (GST)).

[0035] In cases where eukaryotic cells are used as the host cells, an expression vector for eukaryotic cells having a promoter, splicing site, poly(A) addition site and/or the like is used as the expression vector. Examples of such an expression vector include pKA1 pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pcDNA3, pMSG and pYES2. In the same manner as described above, by incorporating a DNA encoding the above polypeptide into such an expression vector and transforming eukaryotic host cells with the vector, followed by culturing the resulting transformants, the polypeptide encoded by the DNA can be expressed in the eukaryotic host cells. In cases where pIND/V5-His, pFLAG-CMV-2, pEGFP-N1, pEGFP-C1 or the like is used as the expression vector, the above polypeptide can be expressed as a fusion protein to which a tag such as His tag (e.g., (His)6 to $(His)_{10}$), FLAG tag, myc tag, HA tag or GFP was added.

[0036] For the introduction of the expression vector into the host cells, well-known methods such as electroporation, the calcium phosphate method, the liposome method, the DEAE dextran method and microinjection can be used.

[0037] Isolation and purification of the polypeptide of interest from the host cells can be carried out by a combination of known separation operations. Examples of the known separation operations include, but are not limited to, treatment with a denaturant such as urea, or a surfactant; ultrasonication treatment; enzyme digestion; salting-out or solvent fractional precipitation; dialysis; centrifugation; ultrafiltration; gel filtration; SDS-PAGE; isoelectric focusing; ion-exchange chromatography; hydrophobic chromatography; affinity chromatography; and reversed-phase chromatography.

[0038] The polypeptides obtained by the above method include, as mentioned above, those in the form of a fusion protein with another arbitrary protein. Examples thereof include fusion proteins with glutathion S-transferase (GST) and with a His tag. Such a polypeptide in the form of a fusion protein is also described herein. Further, in some cases, a polypeptide expressed in a transformed cell is modified in various ways in the cell after translation thereof. Such a polypeptide modified after translation thereof is also included within the scope of the present invention as long as it has an immunity-inducing activity. Examples of such a post-translational modification include elimination of N-terminus methionine, N-terminus acetylation, glycosylation, limited degradation by an intracellular protease, myristoylation, isoprenylation and phosphorylation.

<Immunity-inducing Agent>

[0039] As described concretely in the following Examples, the above-described polypeptide having an immunity-inducing activity can cause regression of an already occurred tumor when administered to a tumor-bearing animal. Therefore, the immunity-inducing agent of the present invention can be used as a therapeutic and/or prophylactic agent for breast cancer and/or leukemia.

[0040] The terms "cancer" and "tumor" used in the present specification mean a malignant neoplasm, and are used interchangeably.

[0041] In this case, cancers to be treated are those expressing the CD179b gene, such as cancers expressing the gene encoding the polypeptide of SEQ ID NO: 3, 5, 7, 9, 11, 13, 15, ..., 93 or 95, and are breast cancer and/or leukemia Examples of other cancers described herein include, breast cancers (mammary gland cancer, combined mammary gland cancer, mammary gland malignant mixed tumor, intraductal papillary adenocarcinoma and the like), leukemias (chronic lymphocytic leukemia and the like), lymphomas (gastrointestinal lymphoma, digestive organ lymphoma, small/medium cell lymphoma and the like).

[0042] The above-described polypeptide, or a recombinant vector comprising a polynucleotide encoding the polypeptide and capable of expressing the polypeptide in vivo can be used as a therapeutic method for immune induction. Further, it can be used as a therapeutic method for the purpose(s) of therapy and/or prophylaxis of animal cancer, and can also be used as a therapeutic method further comprising an immunoenhancer.

[0043] The subject animal is a mammal such as a primate, pet animal, domestic animal or sport animal, preferably human, dog or cat.

[0044] The administration route of the immunity-inducing agent of the present invention to a living body may be either oral administration or parenteral administration, and is preferably parenteral administration such as intramuscular administration, subcutaneous administration, intravenous administration or intraarterial administration. In cases where the immunity-inducing agent is used for therapy of cancer, it may be administered to a regional lymph node in the vicinity of the tumor to be treated, as described in the Examples below, in order to enhance its anticancer activity. The dose may be any dose as long as the dose is effective for immune induction, and, for example, in cases where the agent is

used for therapy and/or prophylaxis of cancer, the dose may be one effective for therapy and/or prophylaxis of the cancer. Further, the dose may vary depending on the body weight, sex (male or female), symptoms and the like. The dose effective for therapy and/or prophylaxis of cancer is appropriately selected depending on the size of the tumor, the symptom and the like, and usually, 0.0001 μg to 1000 μg, preferably 0.001 μg to 1000 μg per subject animal per day, which may be administered once or in several times. The agent is preferably administered in several times, every several days to several months.

[0045] As concretely shown in the Examples below, the immunity-inducing agent of the present invention can cause reduction or regression of an already occurred tumor. Therefore, since the agent can exert its anticancer activity also against a small number of cancer cells in the early stage, development or recurrence of cancer can be prevented by using the agent before development of the cancer or after therapy for the cancer. That is, the immunity-inducing agent of the present invention is effective for both therapy and prophylaxis of cancer.

[0046] The immunity-inducing agent of the present invention may contain only a polypeptide or may be formulated by mixing as appropriate with an additive such as a pharmaceutically acceptable carrier, diluent or vehicle suitable for each administration mode. Formulation methods and additives which may be used are well-known in the field of formulation of pharmaceuticals, and any of the methods and additives may be used. Specific examples of the additives include, but are not limited to, diluents such as physiological buffer solutions; vehicles such as sucrose, lactose, corn starch, calcium phosphate, sorbitol and glycine; binders such as syrup, gelatin, gum arabic, sorbitol, polyvinyl chloride and tragacanth; and lubricants such as magnesium stearate, polyethylene glycol, talc and silica. Examples of the formulation include oral preparations such as tablets, capsules, granules, powders and syrups; and parenteral preparations such as inhalants, injection solutions, suppositories and solutions. These formulations may be prepared by commonly known production methods.

[0047] The immunity-inducing agent of the present invention may be used in combination with an immunoenhancer capable of enhancing the immune response in a living body. The immunoenhancer may be contained in the immunity-inducing agent of the present invention or administered as a separate composition to a patient in combination with the immunity-inducing agent of the present invention.

[0048] Here, the patient is an animal, especially a mammal, preferably human, dog or cat.

[0049] Examples of the immunoenhancer include adjuvants. Adjuvants can enhance the immune response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes, thereby enhancing the immune response and hence the anticancer action. Therefore, especially in cases where the immunity-inducing agent of the present invention is used for therapy and/or prophylaxis of cancer, the immunity-inducing agent preferably comprises an adjuvant, in addition to the above-described polypeptide as an effective ingredient. Many types of adjuvants are well-known in the art, and any of these adjuvants may be used. Specific examples of the adjuvants include MPL (SmithKline Beecham) and homologues of *Salmonella minnesota* Re 595 lipopolysaccharide obtained after purification and acid hydrolysis of the lipopolysaccharide; QS21 (SmithKline Beecham), pure QA-21 saponin purified from an extract of *Quillja saponaria*; DQS21 described in WO96/33739 (SmithKline Beecham); QS-7, QS-17, QS-18 and QS-L1 (So et al., "Molecules and cells", 1997, Vol. 7, p. 178-186); Freund's incomplete adjuvant; Freund's complete adjuvant; vitamin E; Montanide; alum; CpG oligonucleotides (for example, Kreig et al., Nature, Vol. 374, p. 546-549); poly-I:C and derivatives thereof (e.g., poly ICLC); and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Among these, Freund's incomplete adjuvant; Montanide; poly-I:C and derivatives thereof; and CpG oligonucleotides are preferred. The mixing ratio between the above-described adjuvant and the polypeptide is typically about 1:10 to 10:1, preferably about 1:5 to 5:1, more preferably about 1:1. However, the adjuvant is not limited to the above-described examples, and adjuvants known in the art other than those described above (for example, Goding, "Monoclonal Antibodies: Principles and Practice, 2nd edition", 1986) may be used when the immunity-inducing agent of the present invention is administered. Preparation methods for mixtures or emulsions of a polypeptide and an adjuvant are well-known to those skilled in the art of vaccination.

[0050] Further, in addition to the above-described adjuvants, factors that stimulate the immune response of the subject may be used as the above-described immunoenhancer. For example, various cytokines having a property to stimulate lymphocytes and/or antigen-presenting cells may be used as the immunoenhancer in combination with the immunity-inducing agent of the present invention. A number of such cytokines capable of enhancing the immune response are known to those skilled in the art, and examples thereof include, but are not limited to, interleukin-12 (IL-12), GM-CSF, IL-18, interferon-α, interferon-β, interferon, interferon-γ, and Flt3 ligand, which have been shown to enhance the prophylactic action of vaccines. Such factors may also be used as the above-described immunoenhancer, and can be contained in the immunity-inducing agent of the present invention, or can be prepared as a separate composition to be used in combination with the immunity-inducing agent of the present invention, to be administered to a patient

<Antigen-presenting Cells>

[0051] As concretely described in the Examples below, by bringing the above-described polypeptide used in the

present invention into contact with antigen-presenting cells in vitro, the antigen-presenting cells can be made to present the polypeptide. That is, the polypeptides (a) to (c) described above can be used as agents for treating antigen-presenting cells. Examples of the antigen-presenting cells include dendritic cells and B cells, and dendritic cells and B cells having MHC class I molecules are preferably employed. The agents for treating antigen-presenting cells mean agents for pulsing antigen-presenting cells, and, since pulsed antigen-presenting cells can have an ability to stimulate peripheral blood lymphocytes, the cells can be used as a vaccine.

[0052] Various MHC class I molecules have been identified and well-known. MHC molecules in human are called HLA. Examples of HLA class I molecules include HLA-A, HLA-B and HLA-C, more specifically, HLA-A1, HLA-A0201, HLA-A0204, HLA-A0205, HLA-A0206, HLA-A0207, HLA-A11, HLA-A24, HLA-A31, HLA-A6801, HLA-B7, HLA-B8, HLA-B2705, HLA-B37, HLA-Cw0401 and HLA-Cw0602.

[0053] The dendritic cells or B cells having MHC class I molecules can be prepared from peripheral blood by a well-known method. For example, tumor-specific dendritic cells can be induced by inducing dendritic cells from bone marrow, umbilical cord blood or patient's peripheral blood using granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 (or IL-4), and then adding a tumor-related peptide to the culture system.

[0054] By administering an effective amount of such dendritic cells, a response desired for therapy of a cancer can be induced. As the cells to be used, bone marrow or umbilical cord blood donated by a healthy individual, or bone marrow, peripheral blood or the like from the patient himself may be used. When autologous cells of the patient are used, high safety can be attained and serious side effects are expected to be avoided. The peripheral blood or bone marrow may be a fresh sample, cold-stored sample or frozen sample. As for the peripheral blood, whole blood may be cultured or the leukocyte components alone may be separated and cultured, and the latter is efficient and thus preferred. Further, among the leukocyte components, mononuclear cells may be separated. In cases where the cells are originated from bone marrow or umbilical cord blood, the whole cells constituting the bone marrow may be cultured, or mononuclear cells may be separated therefrom and cultured. Peripheral blood, the leukocyte components thereof and bone marrow cells contain mononuclear cells, hematopoietic stem cells and immature dendritic cells, from which dendritic cells are originated, and also CD4-positive cells and the like. As for the cytokine to be used, the production method thereof is not restricted and naturally-occurring or recombinant cytokine or the like may be employed as long as its safety and physiological activity have been confirmed. Preferably, a preparation with assured quality for medical use is used in a minimum necessary amount. The concentration of the cytokine(s) to be added is not restricted as long as the dendritic cells are induced, and usually, the total concentration of the cytokine(s) is preferably about 10 to 1000 ng/mL, more preferably about 20 to 500 ng/mL. The culture may be carried out using a well-known medium usually used for culture of leukocytes. The culturing temperature is not restricted as long as the proliferation of the leukocytes is attained, and about 37°C which is the body temperature of human is most preferred. The atmospheric environment during the culturing is not restricted as long as the proliferation of the leukocytes is attained, and 5% CO_2 is preferably allowed to flow. The culturing period is not restricted as long as a necessary number of the cells is induced therewith, and is usually 3 days to 2 weeks. As for the apparatuses used for separation and culturing of the cells, appropriate apparatuses, preferably those whose safety when applied to medical uses have been confirmed, and whose operations are stable and simple, may be employed. In particular, as for the cell-culturing apparatus, not only the general vessels such as a Petri dish, flask and bottle, but also a layer type vessel, multistage vessel, roller bottle, spinner type bottle, bag type culturing vessel, hollow fiber column and the like may be used.

[0055] Bringing the above-described peptide into contact with the antigen presenting cells in vitro may be carried out by a well-known method. For example, it may be carried out by culturing the antigen-presenting cells in a culture medium containing the above-described polypeptide. The concentration of the peptide in the medium is not restricted, and usually about 1 μg/ml to 100 μg/ml, preferably about 5 μg/ml to 20 μg/ml. The cell density during the culturing is not restricted and usually about 10^3 cells/ml to 10^7 cells/ml, preferably about 5×10^4 cells/ml to 5×10^6 cells/ml. The culturing may be carried out according to a conventional method, and is preferably carried out at 37°C under atmosphere of 5% CO_2. The maximum length of the peptide which can be presented on the surface of the antigen-presenting cells is usually about 30 amino acid residues. Therefore, in cases where the antigen-presenting cells are brought into contact with the polypeptide in vitro, the polypeptide may be prepared such that its length is not more than about 30 amino acid residues, although the length is not restricted.

[0056] By culturing the antigen-presenting cells in the coexistence of the above-described polypeptide, the polypeptide is incorporated into MHC molecules of the antigen-presenting cells and presented on the surface of the antigen-presenting cells. Therefore, using the above-described polypeptide, isolated antigen-presenting cells containing the complex between the polypeptide and the MHC molecules can be prepared. Such antigen-presenting cells can present the polypeptide against T cells in vivo or in vitro, and thereby induce, and allow proliferation of, cytotoxic T cells specific to the polypeptide.

[0057] By bringing the antigen-presenting cells prepared as described above having the complex between the above-described polypeptide and the MHC molecules into contact with T cells in vitro, cytotoxic T cells specific to the polypeptide can be induced and allowed to proliferate. This may be carried out by cocultivating the above-described antigen-presenting

cells and T cells in a liquid medium. For example, it may be attained by suspending the antigen-presenting cells in a liquid medium, placing the suspension in vessels such as wells of a microplate, adding thereto T cells and then culturing the cells. The mixing ratio of the antigen-presenting cells to the T cells in the cocultivation is not restricted, and is usually about 1:1 to 1:100, preferably about 1:5 to 1:20 in terms of the ratio between the numbers of cells. The density of the antigen-presenting cells to be suspended in the liquid medium is not restricted, and is usually about 100 to 10,000,000 cells/ml, preferably about 10,000 to 1,000,000 cells/ml. The cocultivation is preferably carried out at 37°C under atmosphere of 5% CO_2 in accordance with a conventional method. The culturing time is not restricted, and is usually 2 days to 3 weeks, preferably about 4 days to 2 weeks. The cocultivation is preferably carried out in the presence of one or more interleukins such as IL-2, IL-6, IL-7 and/or IL-12. In this case, the concentration of IL-2 and IL-7 is usually about 5 U/ml to 20 U/ml, the concentration of IL-6 is usually about 500 U/ml to 2000 U/ml, and the concentration of IL-12 is usually about 5 ng/ml to 20 ng/ml, but the concentrations of the interleukins are not restricted thereto. Here, "U" indicates the unit of activity. The above cocultivation may be repeated once to several times adding fresh antigen-presenting cells. For example, the operation of discarding the culture supernatant after the cocultivation and adding a fresh suspension of antigen-presenting cells to further conduct the cocultivation may be repeated once to several times. The conditions of the each cocultivation may be the same as described above.

[0058] By the above-described cocultivation, cytotoxic T cells specific to the polypeptide are induced and allowed to proliferate. Thus, using the above-described polypeptide, isolated T cells can be prepared which selectively bind the complex between the polypeptide and the MHC molecule.

[0059] As described in the Examples below, the genes encoding the polypeptides of SEQ ID NOs:3, 5, 7, 9, 11, 13, 15, ..., 93 and 95 are expressed specifically in breast cancer cells, leukemia cells and lymphoma cells. Therefore, it is thought that, in these cancer species, significantly higher numbers of the polypeptides of SEQ ID NOs:3, 5, 7, 9, 11, 13, 15, ..., 93 and 95 exist than in normal cells. When cytotoxic T cells prepared as described above are administered to a living body while a part of the polypeptides existing in cancer cells are presented by MHC molecules on the surfaces of the cancer cells, the cytotoxic T cells can damage the cancer cells using the presented polypeptides as markers. Since antigen-presenting cells presenting the above-described polypeptides can induce, and allow proliferation of, cytotoxic T cells specific to the polypeptides also in vivo, cancer cells can be damaged also by administering the antigen-presenting cells to a living body. That is, the cytotoxic T cells and the antigen-presenting cells prepared using the polypeptide are also effective as therapeutic and/or prophylactic agents for cancer, similarly to the immunity-inducing agent of the present invention.

[0060] In cases where the above-described isolated antigen-presenting cells or isolated T cells are administered to a living body, these are preferably prepared by treating antigen presenting cells or T cells collected from the patient to be treated with the polypeptide (a) to (c) as described above in order to avoid the immune response in the living body that attacks these cells as foreign bodies.

[0061] The therapeutic and/or prophylactic agent for cancer comprising as an effective ingredient the antigen-presenting cells or T cells is preferably administered via a parenteral administration route such as intravenous or intraarterial administration. The dose is appropriately selected depending on the symptom, the purpose of administration and the like, and is usually 1 cell to 10,000,000,000,000 cells, preferably 1,000,000 cells to 1,000,000,000 cells, which dose is preferably administered once per several days to once per several months. The formulation may be, for example, the cells suspended in physiological buffered saline, and the formulation may be used in combination with another/other anticancer preparation(s) and/or cytokine(s). Further, one or more additives well-known in the field of formulation of pharmaceuticals may also be added.

<Gene Vaccine>

[0062] Also by expression of the polynucleotide encoding the polypeptide (a) to (c) in the body of the subject animal, antibody production and cytotoxic T cells can be induced in the living body, and an effect comparable to that obtained in the case of administration of a polypeptide can be obtained. That is, the immunity-inducing agent of the present invention may be one comprising as an effective ingredient a recombinant vector having a polynucleotide encoding the polynucleotide (a) to (c), which recombinant vector is capable of expressing the polypeptide in a living body. Such a recombinant vector capable of expressing an antigenic polypeptide is also called gene vaccine.

[0063] The vector used for production of a gene vaccine is not restricted as long as it is a vector capable of expressing a polypeptide in a cell of the subject animal (preferably in a mammalian cell), and may be either a plasmid vector or a virus vector, and any known vector in the field of gene vaccines may be used. The polynucleotide such as DNA or RNA encoding the above-described polypeptide can be easily prepared, as mentioned above, by a conventional method. Incorporation of the polynucleotide into the vector can be carried out using a method well-known to those skilled in the art.

[0064] The administration route of the gene vaccine is preferably a parenteral route such as intramuscular, subcutaneous, intravenous or intraarterial administration, and the dose may be appropriately selected depending on the type of the antigen and the like, and usually about 0.1 μg to 100 mg, preferably about 1 μg to 10 mg in terms of the weight

of the gene vaccine per 1 kg of body weight.

[0065] Methods using a virus vector include those wherein a polynucleotide encoding the above-described polypeptide is incorporated into an RNA virus or DNA virus, such as a retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, pox virus, poliovirus or Sindbis virus, and then the subject animal is infected with the resulting virus. Among these methods, those using a retrovirus, adenovirus, adeno-associated virus, vaccinia virus or the like are especially preferred.

[0066] Examples of other methods include a method wherein an expression plasmid is directly intramuscularly administered (DNA vaccine method), the liposome method, lipofectin method, microinjection method, calcium phosphate method and electroporation method, and the DNA vaccine method and liposome method are especially preferred.

[0067] Methods for actually making the gene encoding the above-described polypeptide used in the present invention act as a pharmaceutical include the in vivo method wherein the gene is directly transfected into the body, and the ex vivo method wherein a kind of cells are collected from the subject animal and the gene is transfected into the cells ex vivo, followed by returning the cells to the body (Nikkei Science, 1994, April, p. 20-45; The Pharmaceutical Monthly, 1994, Vol. 36, No. 1, p. 23-48; Experimental Medicine, Extra Edition, 1994, Vol.12, No. 15; and references cited in these papers and the like). The in vivo method is more preferred.

[0068] In cases where the gene is administered by the in vivo method, the gene may be administered through an appropriate administration route depending on the disease to be treated, symptom and so on. It may be administered by, for example, intravenous, intraarterial, subcutaneous, intramuscular administration or the like, or may be directly administered to the affected area in which a tumor exists. In cases where the gene is administered by the in vivo method, the gene may be formulated into a preparation such as a solution, and in general, it is formulated into an injection solution or the like containing DNA encoding the above-described peptide of the present invention as an effective ingredient. A commonly used carrier(s) may be added thereto as required. In the case of a liposome or membrane fusion liposome (Sendai virus (HVJ)-liposome or the like) containing the DNA, the liposome may be formulated into a liposome preparation such as a suspension, frozen preparation or centrifugally concentrated frozen preparation.

[0069] In the present invention, "the base sequence shown in SEQ ID NO:1" includes not only the base sequence expressly written in SEQ ID NO:1, but also the sequence complementary thereto. Thus, "a polynucleotide having the base sequence shown in SEQ ID NO:1" includes a single-stranded polynucleotide having the base sequence expressly written in SEQ ID NO:1, a single-stranded polynucleotide having the base sequence complementary thereto, and a double-stranded polynucleotide composed of these single-stranded polynucleotides. When the polynucleotide encoding the polypeptide used in the present invention is prepared, any one of these base sequences should be appropriately selected, and those skilled in the art can easily carry out the selection.

<Detection of Cancer>

[0070] In a method of the present invention for detection of breast cancer and/or leukemia, expression of the polypeptide used in the present invention is measured using a sample separated from a living body. The method for measuring the expression of a polypeptide using the sample includes a method in which an antibody against the polypeptide, which antibody is contained in the sample, is measured by immunoassay (Method 1); a method in which the polypeptide per se contained in the sample is measured by immunoassay (Method 2); and a method in which mRNA contained in the sample which encodes the polypeptide is measured (Method 3). In the method of the present invention, the expression of the polypeptide may be measured by any of these three methods. In the present invention, the term "measurement" includes detection, quantification and semi-quantification.

[0071] Here, CD179b was identified as a polypeptide which binds to an antibody (cancer-specific antibody) specifically existing in serum derived from a tumor-bearing dog, by the SEREX method using serum from a canine patient from which a canine breast cancer-derived cDNA library was prepared (see Example 1). That is, in the living body of a tumor-bearing dog, an antibody against CD179b is specifically induced. Thus, also by measuring an antibody against CD179b in a tumor-bearing living body, a cancer expressing CD179b can be detected (see Example 7). Further, a canine cancer can be detected also by measuring CD179b as an antigen by the above Method 2. Further, since, as described in the Examples below, mRNA encoding the antigen polypeptide is significantly more highly expressed in cancer, especially in breast cancer and leukemia cells, than in normal tissues (see Example 1), a canine cancer can be detected also by measuring the mRNA. As mentioned above, CD 179b is known to be expressed on the membrane surfaces of precursor cells of B cells (pre-B cells), and therefore it is reported that CD179b is expressed in leukemia (pre-B cell leukemia) cells derived by cancerization of pre-B cells, but the fact that leukemia cells other than pre-B cell leukemia cells and breast cancer cells show expression of CD179b was first discovered in the present invention. Accordingly, detection of leukemia other than pre-B cell leukemia cells and breast cancer became possible by investigating expression of CD179b.

[0072] In Method 1 above, measurement of the cancer-specific antibody which may exist in the sample can be easily carried out by immunoassay using an antigenic substance which immunologically reacts with the antibody. The immunoassay per se is a conventional well-known method as explained in detail below. As the antigenic substance which

may be used in the immunoassay, the polypeptide (a) to (c) may be used. As antibodies have cross-reactivity, a molecule may be bound to an antibody which is induced against another immunogen, as long as the molecule has any structure thereon which is similar to the epitope of the immunogen. For example, polypeptides having high amino acid sequence homology to each other often have epitopes with similar structures, and in such cases the both polypeptides may have the same antigenicity. As concretely described in the Examples below, the human-derived polypeptide of SEQ ID NO:3 immunologically reacts with the antibody induced in the body of a tumor-bearing dog. Therefore, in Method 1 of the present invention, any mammalian homologous factor may be used as an antigen in the immunoassay.

[0073] Antigenic substances having a large molecular weight and a complex structure, such as proteins, usually have a plurality of sites with different structures on their surface. Therefore, such an antigenic substance induces a plurality of kinds of antibodies which respectively recognize each of the sites in a living body. That is, an antibody induced in a living body against an antigenic substance such as a protein is a polyclonal antibody, which is a mixture of a plurality of kinds of antibodies. It should be noted that, in the present invention, the term "polyclonal antibody" means an antibody which exists in serum derived from a living body having an antigenic substance therein and is induced in the living body against the antigenic substance.

[0074] Measurement of the antibody in a sample may easily be carried out by immunoassay using the above-described polypeptide as an antigen. Immunoassays per se are well-known in the art, and includes, when classified based on the reaction mode, the sandwich method, competition method, agglutination method, Western blotting and the like. When classified based on the label, immunoassays include radioimmunoassay, fluorescence immunoassay, enzyme immunoassay, biotin immunoassay and the like, and the immunoassay of the above-described antibody may be carried out by any of these immunoassays. Although not restricted, the sandwich ELISA and agglutination method may be preferably used as an immunoassay of the above antibody in the present invention, as these methods are simple and do not require a large-scale apparatus. In cases where an enzyme is used as a label of an antibody, the used enzyme is not particularly restricted as long as it satisfies such conditions that the turnover number is large, that the enzyme is stable even when it is bound to an antibody, that it specifically colors its substrate and the like. For example, enzymes used in an ordinary enzyme immunoassay such as peroxidase, β-galactosidase, alkaline phosphatase, glucose oxidase, acetylcholinesterase, glucose-6-phosphate dehydrogenase, and malate dehydrogenase may be used. Enzyme inhibitors, coenzymes and the like may also be used. Binding of these enzymes with an antibody may be carried out by a known method using a cross-linking agent such as a maleimide compound. As a substrate, known substances may be used depending on the kind of the used enzyme. For example, in cases where peroxidase is used as the enzyme, 3,3',5,5'-tetramethylbenzidine may be used; and in cases where alkaline phosphatase is used as the enzyme, para-nitrophenol or the like may be used. As the radioisotope, those used in an ordinary radioimmunoassay such as ^{125}I or ^{3}H may be used. As the fluorescent dye, one used in an ordinary fluorescent antibody technique, such as fluorescein isothiocyanate (FITC), tetramethylrhodamine isothiocyanate (TRITC) or the like may be used.

[0075] These immunoassays per se are well-known in the art, and so it is not necessary to explain these immunoassays in the present specification. Briefly, in sandwich immunoassays, for example, the above-mentioned polypeptide used as an antigen is immobilized on a solid phase, and then reacted with a sample such as a serum. After washing the solid phase, the resultant is reacted with an appropriate secondary antibody. After washing the solid phase, the secondary antibody bound to the solid phase is measured. In the method for detecting cancer according to the present invention, it is preferred to immobilize an antigen polypeptide on a solid phase, because immobilization on a solid phase makes it possible to easily remove the unbound secondary antibody. As the secondary antibody, for example, anti-dog IgG antibody may be used in cases where the sample is obtained from dogs. The secondary antibody bound to the solid phase may be measured by labeling the secondary antibody with a labeling substance exemplified above. The thus measured amount of the secondary antibody corresponds to the amount of the above-mentioned antibody in a serum sample. In cases where an enzyme is used as the labeling substance, the amount of the antibody may be measured by adding a substrate which is decomposed by the enzymatic activity to develop a color, and then optically measuring the amount of decomposed substrate. In cases where a radioisotope is used as the labeling substance, the amount of radiation from the radioisotope may be measured with a scintillation counter or the like.

[0076] In Method 2 of the present invention, the polypeptide shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 is measured, which polypeptide may be contained in the sample obtained from a living body. As explained above, the abundance of the cancer-specific antibody which immunologically reacts with the polypeptide shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 or a homologous factor thereof is significantly high in cancer patients, which indicates that the production of the polypeptide or a homologous factor thereof, which is the antigen of the cancer-specific antibody, is significantly high in the cancer patients. Therefore, similarly to Method 1 above, cancers in a living body can be detected by measuring the polypeptide shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 or a homologous factor thereof.

[0077] Measurement of the polypeptide in a sample may easily be carried out by a well-known immunoassay. Specifically, for example, the polypeptide having the amino acid sequence shown in the odd number ID of SEQ ID NOs:3 to 95 or a homologous factor thereof which may exist in a sample may be measured by preparing an antibody or antigen-binding fragment thereof which immunologically reacts with the polypeptide having the amino acid sequence shown in

the odd number ID of SEQ ID NOs:3 to 95 or a homologous factor thereof, and then carrying out an immunoassay using the prepared antibody or fragment thereof. The immunoassay per se is a well-known conventional method as described above.

[0078] The term "antigen-binding fragment" herein means an antibody fragment such as the Fab fragment or the $F(ab')_2$ fragment contained in an antibody molecule, which has a binding capacity to an antigen. Although the antibody may be either a polyclonal antibody or monoclonal antibody, a monoclonal antibody is preferred for immunoassays and the like, because a high reproducibility is attained therewith. Methods for preparing a polyclonal or monoclonal antibody using a polypeptide as an immunogen are well-known, and the preparation may be easily carried out by a conventional method. For example, antibodies against the polypeptide may be induced by immunizing an animal with an immunogen, the polypeptide conjugated to a carrier protein such as keyhole limpet hemocyanin (KLH) or casein, together with an adjuvant. Then antibody-producing cells such as spleen cells or lymphocytes are collected from the immunized animal and fused with myeloma cells to prepare hybridomas. Among the hybridomas, one producing an antibody which binds to the polypeptide shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 or a homologous factor thereof is selected and proliferated, and then the monoclonal antibody whose corresponding antigen is the above-mentioned protein may be collected from the culture supernatant. The above-described method is a conventional well-known method.

[0079] In Method 3 of the present invention, mRNA encoding CD179b, which may be contained in a sample obtained from a living body, is measured. As concretely described in the Examples below, the expression level of mRNA encoding CD179b is significantly high in cancer, especially, breast cancer and leukemia cells. Therefore, cancers in a living body can be detected by measuring the mRNA in a sample.

[0080] In the detection method of the present invention, whether the subject living body suffers from breast cancer and/or leukemia or not or the like is determined based on the expression level of the polypeptide measured as described above. Although the cancer detection may be attained simply by measuring the expression of the polypeptide in the subject living body, it is preferred to obtain the normal reference value by determining the expression level of the polypeptide (the amount of the antibody, polypeptide or mRNA) in one or more samples from healthy individuals to compare the measured value in the subject living body with the normal reference value, in view of increasing the detection accuracy. In order to further increase the detection accuracy, the cancer reference value may be obtained by determining the expression level of the polypeptide in samples obtained from many patients who have been revealed to suffer from cancer to compare the measured value of the subject living body with the both of the normal and cancer reference values. The above mentioned reference values may be determined by expressing the expression level of the polypeptide in each sample in values and calculating the average value thereof. The normal and cancer reference values may be determined beforehand by measuring the expression level of the polypeptide in many healthy and cancer subjects. Thus, when the measured value is compared with the reference values in the method of the present invention, the reference values may be those predetermined.

[0081] The detection method of the present invention may be carried out in combination with detection using other cancer antigens and/or cancer markers so that the detection accuracy of cancers can be more improved.

[0082] By the detection method of the present invention, breast cancer and/or leukemias in a living body can be detected. The method of the present invention can detect even an invisible small tumor or a tumor which exists in a deep part of a body, and thus the method is useful for early detection of cancer. Further, by applying the detection method of the present invention to patients in the follow-up period after cancer therapy, the recurrent cancer, if any, can be detect in its early stage.

[0083] If the more cancer cells expressing the prescribed polypeptide to be measured in the present invention proliferate in a tumor-bearing living body, the more the polypeptides and mRNAs encoding them accumulate in the body, which causes the increased amount of the antibodies against the above-mentioned polypeptides in the serum. On the other hand, the more cancer cells decrease, the more the accumulated polypeptides and mRNAs encoding them decrease in the living body, which causes the decreased amount of the antibodies against the above-mentioned polypeptides in the serum. Thus, if the expression level of the prescribed polypeptide is high, it can be determined that tumor growth and/or metastasis of cancer occurred, i.e., the stage of progression of cancer is advanced.

[0084] Further, as shown in the Example below, when compared between the same kinds of tumors, a malignant one produces significantly higher amount of the antibodies than a benign one. Therefore, if the expression level of the prescribed polypeptides is high, it can be determined that the grade of cancer malignancy is higher. That is, the grade of cancer malignancy can also be detected by the method of the present invention.

[0085] Furthermore, the effect of the cancer therapy can be monitored based on the increase or decrease in the expression level of the prescribed polypeptides. Therefore, by observing the expression level of the above-mentioned polypeptides on an individual during or after cancer therapy, a clue to assess how much the administered anti-cancer agent was effective, or whether a portion of the tumor is left in the patient after extirpation of the tumor can be obtained, as well as a clue to find metastasis and/or recurrence as early as possible can be obtained during the follow-up. Appropriate treatment of cancer results in decrease in the expression level of the polypeptides compared to that in the tumor-bearing state before the therapy. In such a case, it can be judged that the effect of the therapy which was (is being) performed

on the living body is/was good. In cases where the expression level of the polypeptides increases or is sustained, or once decreases and then increases, it can be judged that the effect of the therapy is not good enough. This may be a useful basis for selection of a therapeutic method, such as decision to change the therapeutic method or to change the dose of an anti-cancer agent.

[0086] Cancers to be detected by the method of the present invention are those expressing CD179b (excluding pre-B cell tumors), and examples thereof include mammary gland cancer, combined mammary gland cancer, mammary gland malignant mixed tumor, intraductal papillary adenocarcinoma, and/or leukemias (preferably, chronic lymphocytic leukemia excluding those of the pre-B cell type). The living bodies to which the method of the present invention applies are mammals, preferably humans, dogs and cats.

[0087] The sample to be subjected to the method of the present invention includes body fluids such as blood, serum, plasma, ascites and pleural effusion; tissues; and cells. In particular, serum, plasma, ascites and pleural effusion may be preferably used in Method 1 and Method 2 above. A tissue sample and cell sample are preferred in the case of Method 3 above in which mRNA is measured.

[0088] The polypeptide used as an antigen for immunoassay in Method 1 may be provided as a reagent for detecting breast cancer and/or leukemia. The reagent may consist only of the above-mentioned polypeptide, or may contain various additives useful for stabilizing the polypeptide, and the like. The reagent may also be provided in the form of being immobilized on a solid phase such as a plate or membrane.

[0089] The antibody or an antigen-binding fragment thereof which immunologically reacts with the polypeptide of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, ..., 93 or 95 or a homologous factor thereof, which is used for measuring the polypeptide or the homologous factor thereof by immunoassay in Method 2, may also be provided as a reagent for detecting cancer. The reagent may also consist only of the above-mentioned antibody or antigen-binding fragment thereof, or may contain various additives useful for stabilizing the antibody or antigen-binding fragment thereof, and the like. The antibody or antigen-binding fragment thereof may also be in the form of being conjugated with a metal such as manganese or iron. Since such a metal-conjugated antibody or antigen-binding fragment thereof accumulates in a site in which a large amount of antigen protein exists when administered to a body, the existence of cancer cells which produce the antigen protein can be detected by measuring the metal by MRI or the like.

[0090] Furthermore, the above-described polynucleotide for cancer detection used for measuring mRNA in Method 3 may also be provided as a reagent for detecting cancer. The reagent for detecting cancer may also consist only of the polynucleotide, or may contain various additives useful for stabilizing the polynucleotide and the like. The polynucleotide for cancer detection contained in the reagent is preferably a primer or a probe.

EXAMPLES

[0091] The present invention will now be described more concretely by way of Examples.

Example 1: Acquisition of Novel Cancer Antigen Protein by SEREX Method

(1) Preparation of cDNA Library

[0092] From a canine mammary gland cancer tissue removed by surgery, total RNA was extracted by the Acid guanidium-Phenol-Chloroform method, and poly(A)$^+$ RNA was purified using the Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) according to the protocol described in the attached instructions.

[0093] Using the obtained mRNA (5 μg), a canine mammary gland cancer-derived cDNA phage library was synthesized. Preparation of the cDNA phage library was carried out using cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by STRATAGENE) in accordance with the protocols attached to the kits. The size of the prepared cDNA phage library was 2.99×10^5 pfu/ml.

(2) Screening of cDNA Library with Serum

[0094] Using the canine mammary gland cancer-derived cDNA phage library prepared as described above, immunoscreening was carried out. More particularly, host *E. coli* (XL1-Blue MRF') was infected with the library such that 2340 clones were included in a Φ90×15 mm NZY agarose plate, followed by culture at 42°C for 3 to 4 hours to allow formation of plaques. The plate was covered with a nitrocellulose membrane (Hybond C Extra; manufactured by GE Healthcare BioScience) impregnated with IPTG (isopropyl-β-D-thiogalactoside) at 37°C for 4 hours, to allow induction and expression of proteins, thereby transferring the proteins to the membrane. Thereafter, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl pH 7.5) supplemented with 0.5% non-fat dry milk, followed by being shaken at 4°C overnight to suppress nonspecific reactions. This filter was allowed to react with 500-fold diluted canine patient serum at room temperature for 2 to 3 hours.

[0095] As the above-described canine patient serum, a total of 3 serum samples were used which were collected from each of the dog from which the above mammary gland cancer was removed and another mammary gland cancer canine patient. These sera were stored at -80°C and pretreated immediately before use. The pretreatment of the sera was carried out by the following method. That is, host *E. coli* (XL1-BLue MRF') was infected with λ ZAP Express phage into which no exogenous gene was inserted, and cultured on an NZY plate at 37°C overnight. Subsequently, 0.2 M $NaHCO_3$ buffer (pH 8.3) containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C for 15 hours, followed by recovering the supernatant as an *E. coli*/phage extract. Thereafter, the recovered *E. coli*/phage extract was passed through an NHS-column (manufactured by GE Healthcare BioScience) to immobilize the proteins derived from the *E. coli*/phage. The serum from the canine patient was passed through this protein-immobilized column and allowed to react with the proteins, thereby removing antibodies that adsorb to *E. coli* and the phage from the serum. The serum fraction passed through the column without being adsorbed was 500-fold diluted with TBS supplemented with 0.5% non-fat dry milk, and the resulting dilution was used as a material for the immunoscreening.

[0096] The membrane to which the thus treated serum and the above-described fusion proteins were blotted was washed with TBS-T (0.05% Tween 20/TBS) 4 times, and goat anti-dog IgG (Goat anti Dog IgG-h+l HRP conjugated; manufactured by BETHYL Laboratories, Inc.) which was 5000-fold diluted with TBS supplemented with 0.5% non-fat dry milk was allowed, as a secondary antibody, to react at room temperature for 1 hour. Detection was carried out by an enzymatic coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche), and colonies whose positions were identical to those of positive sites of the coloring reaction were collected from the Φ90×15mm NZY agarose plate, and dissolved into 500 μl of SM buffer (100 mM NaCl, 10 mM $MgClSO_4$, 50 mM Tris-HCl, 0.01% gelatin, pH7.5). The second and third screenings were carried out by repeating the same method as described above until the colonies positive in the coloring reaction became single colonies, thereby isolating 45 positive clones after screening of 92820 phage clones reactive with IgG in the serum.

(3) Homology Search of Isolated Antigen Genes

[0097] To subject the 45 positive clones isolated by the above method to sequence analysis, an operation to convert the phage vector to a plasmid vector was carried out. More particularly, 200 μl of a solution prepared such that the host *E. coli* (XL1-Blue MRF') was contained to an absorbance OD_{600} of 1.0, 250 μl of the purified phage solution and 1 μl of ExAssist helper phage (manufactured by STRATAGENE) were mixed together, and the resulting mixture was allowed to react at 37°C for 15 minutes, followed by adding 3 ml of LB broth thereto and culturing the resultant at 37°C for 2.5 to 3 hours. This was immediately followed by 20 minutes of incubation in a water bath at 70°C and centrifugation at 1000×g for 15 minutes, after which the supernatant was collected as a phagemid solution. Subsequently, 200 μl of a solution prepared such that the phagemid host *E. coli* (SOLR) was contained to an absorbance OD_{600} of 1.0 and 10 μl of the purified phagemid solution were mixed together, and the resulting mixture was allowed to react at 37°C for 15 minutes, followed by plating a 50 μl aliquot of the resultant on LB agar medium supplemented with ampicillin (50 μg/ml final concentration) and culturing at 37°C overnight. Single colonies of the transformed SOLR were picked up and cultured in LB medium supplemented with ampicillin (50 μg/ml final concentration) at 37°C, followed by purifying plasmid DNAs having inserts of interest using QIAGEN plasmid Miniprep Kit (manufactured by QIAGEN).

[0098] Each purified plasmid was subjected to analysis of the full-length sequence of the insert by the primer walking method using the T3 primer shown in SEQ ID NO:96 and the T7 primer shown in SEQ ID NO:97. By this sequence analysis, the gene sequences shown in the even number IDs of SEQ ID NOs:4 to 92 were obtained. Using the base sequences and the amino acid sequences (odd number IDs of SEQ ID NOs: 5 to 93) of these genes, homology search against known genes were carried out using a homology search program BLAST (http://www.ncbi.nlm.nih.gov/BLAST/), and, as a result, it was revealed that all the obtained 45 genes were those encoding CD179b. The homologies among the 45 genes were 94 to 99% in terms of the base sequences and 96 to 99% in terms of the amino acid sequences. The homologies between these genes and the gene encoding a human homologous factor were 62 to 82% in terms of the base sequences and 69 to 80% in terms of the amino acid sequences, in the region translated to a protein. The base sequence of the human homologous factor is shown in SEQ ID NO: 1, and the amino acid sequences of the human homologous factor are shown in SEQ ID NOs:2 and 3. Further, the homologies between these genes and the gene encoding a bovine homologous factor were 68 to 82% in terms of the base sequences and 56 to 77% in terms of the amino acid sequences, in the region translated to a protein. The base sequence of the bovine homologous factor is shown in SEQ ID NO:94, and the amino acid sequence of the bovine homologous factor is shown in SEQ ID NO:95. The homology between the gene encoding the human homologous factor and the gene encoding the bovine homologous factor was 62% in terms of the base sequences and 72% in terms of the amino acid sequences, in the region translated to a protein.

(4) Analysis of Expression in Various Tissues

[0099] Expressions of the genes obtained by the above method in canine and human normal tissues and various cell lines were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, from 50 to 100 mg of each tissue or 5-10$\times 10^6$ cells of each cell line, total RNA was extracted using the TRIZOL reagent (manufactured by INVITROGEN) according to the protocol described in the attached instructions. Using this total RNA, cDNA was synthesized by the Superscript First-Strand Synthesis System for RT-PCR (manufactured by INVITROGEN) according to the protocol described in the attached instructions. As the cDNAs of human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by INVITROGEN), QUICK-Clone cDNA (manufactured by CLONETECH) and Large-Insert cDNA Library (manufactured by CLONETECH) were used. The PCR reaction was carried out as follows, using primers specific to the obtained canine genes (shown in SEQ ID NOs:98 and 99) and their human homologous gene (shown in SEQ ID NOs:100 and 101). That is, reagents and an attached buffer were mixed such that concentrations/amounts of 0.25 μl of a sample prepared by the reverse transcription reaction, 2 μM each of the above primers, 0.2 mM each of dNTPs, and 0.65 U ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) were attained in a total volume of 25 μl, and the reaction was carried out with 30 cycles of 94°C for 30 seconds, 60°C for 30 seconds and 72°C for 30 seconds using a Thermal Cycler (manufactured by BIO RAD). The above-described primers specific to genes having the base sequences shown in SEQ ID NOs: 98 and 99 were for amplification of the positions 32 to 341 in the base sequence shown in SEQ ID NO:4, and for amplification of the region common to all the canine CD179b genes shown in the even number IDs of SEQ ID NOs: 4 to 92. Further, the primers specific to genes having the base sequences shown in SEQ ID NOs:100 and 101 were for amplification of the positions 216 to 738 in the base sequence shown in SEQ ID NO: 1. As a control for comparison, primers specific to GAPDH (shown in SEQ ID NOs:102 and 103) were used at the same time. As a result, as shown in Fig. 1, the obtained canine genes did not show expression in normal canine tissues at all, but showed strong expression in canine breast cancer tissues. In terms of expression of the human homologous gene, bone marrow was the only human normal tissue wherein its expression was confirmed, but, in human cancer cells, its expression was detected in leukemia cell lines and breast cancer cell lines, so that specific expression of CD179b in the leukemia cell lines and the breast cancer cell lines was confirmed.

[0100] In Fig. 1, reference numeral 1 in the ordinate represents the expression pattern of the gene identified as described above, and reference numeral 2 represents the expression pattern of the GAPDH gene as the control for comparison.

Example 2: Preparation of Canine and Human Novel Cancer Antigen Protein

(1) Preparation of Recombinant Protein

[0101] Based on the gene of SEQ ID NO:4 obtained in Example 1, a recombinant protein was prepared by the following method. That is, reagents and an attached buffer were mixed such that concentrations/amounts of 1 μl of the vector prepared from the phagemid solution obtained in Example 1 and subjected to the sequence analysis, 0.4 μM each of two kinds of primers having *Nde*I and *Kpn*I restriction sites (described in SEQ ID NOs:104 and 105), 0.2 mM dNTP, and 1.25 U PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) were attained in a total volume of 50 μl, and PCR was carried out with 30 cycles of 98°C for 10 seconds and 68°C for 40 seconds using a Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those for amplification of the region encoding the 5th to 120th amino acids in the amino acid sequence shown in SEQ ID NO:5. After the PCR, the amplified DNA was subjected to electrophoresis using 2% agarose gel, and a DNA fragment of about 350 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0102] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the sequence of the amplified gene fragment matches the sequence of interest. The plasmid having the sequence that matched the sequence of interest was treated with restriction enzymes *Nde*I and *Kpn*I and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli,* pET30b (manufactured by Novagen) that had been treated with restriction enzymes *Nde*I and *Kpn*I. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

[0103] On the other hand, based on the gene of SEQ ID NO: 1, a recombinant protein of the human homologous gene was prepared by the following method. Reagents and an attached buffer were mixed such that concentrations/amounts 1 μl of the cDNA prepared in Example 1 whose expression could be confirmed by the RT-PCR method in cDNAs from various tissues/cells, 0.4 μM each of two kinds of primers having *Eco*RI and *Sal*I restriction sites (described in SEQ ID NOs:106 and 107), 0.2 mM dNTP, and 1.25 U PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.)

were attained in a total volume of 50 μl, and PCR was carried out with 30 cycles of 98°C for 10 seconds and 68°C for 40 seconds using a Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those for amplification of the total length the amino acid sequence shown in SEQ ID NO:3. After the PCR, the amplified DNA was subjected to electrophoresis using 2% agarose gel, and a DNA fragment of about 540 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0104] The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and plasmids were recovered thereafter, followed by confirming, by sequencing, that the sequence of the amplified gene fragment matches the sequence of interest. The plasmid having the sequence that matched the sequence of interest was treated with restriction enzymes *Eco*RI and *Sal*I and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli,* pET30a (manufactured by Novagen) that had been treated with restriction enzymes *Eco*RI and *Sal*I. Usage of this vector enables production of a His-tag fusion recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression of the protein of interest was induced in *E. coli* with 1 mM IPTG.

(2) Purification of Recombinant Protein

[0105] The above-obtained recombinant *E. coli* cells that expresse SEQ ID NO:1 and SEQ ID NO:4, respectively, were cultured in LB medium supplemented with 30 μg/mL kanamycin at 37°C until the absorbance at 600 nm reached about 0.7, and then isopropyl-β-D-1-thiogalactopyranoside was added thereto such that its final concentration should be 1 mM, followed by culturing them at 30°C for 20 hours. Subsequently, the cells were collected by centrifugation at 4,800 rpm for 10 minutes. The pellet of the cells was suspended in phosphate-buffered saline and further subjected to centrifugation at 4,800 rpm for 10 minutes to wash the cells.

[0106] The cells were suspended in phosphate-buffered saline and subjected to sonication on ice. The sonicated solution of *E. coli* was centrifuged at 7,000 rpm for 20 minutes to obtain the supernatant as the soluble fraction and the precipitate as the insoluble fraction.

[0107] The insoluble fraction was suspended in 4% Triton-X100 solution and centrifuged at 7,000 rpm for 20 minutes. This operation was repeated twice and an operation of removal of proteases was carried out.

[0108] The residue was suspended in 20 mM phosphate buffer (pH 8.0) containing 6M guanidine hydrochloride, and the resulting suspension was left to stand at 4°C for 20 hours to denature proteins. Thereafter, the suspension was centrifuged at 7,000 rpm for 20 minutes, and the obtained soluble fraction was placed in a nickel chelate column prepared by a conventional method (carrier: Chelating Sepharose (trademark) Fast Flow (GE Health Care); column volume: 5 mL; equilibration buffer: 20 mM phosphate buffer (pH 8.0) containing 6M guanidine hydrochloride). The fraction that was not adsorbed to the column was washed away with 10 column volumes of 20 mM phosphate buffer (pH 8.0) containing 6M guanidine hydrochloride and 20 mM phosphate buffer (pH 8.0) containing 10 mM imidazole, and elution was immediately carried out with a four-step density gradient of 50 mM-500 mM imidazole, to obtain a purified fraction, which was used thereafter as a material for administration tests.

[0109] To 1 ml of a reaction buffer (20 mM Tris-HCl, 50 mM NaCl, 2 mM $CaCl_2$; pH 7.4), 200 μl of the purified preparation obtained by the above-described method was aliquoted, and 2 μl of enterokinase (manufactured by Novagen) was then added thereto, followed by leaving it to stand at room temperature overnight to cleave His tag. The resulting product was purified using Enterokinase Cleavage Capture Kit (manufactured by Novagen) in accordance with the protocol attached to the kit. Subsequently, the buffer contained in 1.2 ml of the purified preparation obtained by the above-described method was replaced with physiological phosphate buffer (manufactured by Nissui Pharmaceutical) by ultrafiltration using NANOSEP 10K OMEGA (manufactured by PALL), and the resulting solution was filtered aseptically using HT Tuffryn Acrodisc 0.22 μm (manufactured by PALL) and used in the following experiments.

Example 3: Test of Administration of Recombinant Protein to Cancer-bearing Dog

(1) Antitumor Assay

[0110] The anti-tumor effect of the recombinant protein which was purified as described above was assessed in a tumor-bearing dog (breast cancer) having an epidermal tumor.

[0111] An equal amount of Freund's incomplete adjuvant (manufactured by Wako Pure Chemicals) was mixed with 100 μg (0.5 ml) of the recombinant polypeptide purified as described above, to prepare a therapeutic agent for cancer. This was administered to a regional lymph node in the vicinity of the tumor a total of 3 times, by carrying out the subsequent administrations 3 days and 7 days after the first administration. As a result, the tumor with a size of about 55 mm^3 at the time of administration of the therapeutic agent for cancer was reduced in size to 30 mm^3 10 days after the first administration; to 16 mm^3 20 days after the first administration; and to 10 mm^3 30 days after the first administration.

[0112] Further, to another canine patient suffering from mammary gland cancer, a mixture of 100 μg (0.5 ml) of the

above-described polypeptide derived from dog and 0.5 ml of Freund's incomplete adjuvant was administered in the same manner as described above a total of 3 times. Further, concurrently with the respective administrations, 100 μg of canine interleukin 12 was administered subcutaneously. As a result, the tumor with a size of about 155 mm^3 at the time of administration of the therapeutic agent for cancer completely regressed 24 days after the first administration.

(2) Immune Inducibility Assay

[0113] Blood of the canine patient in which the anti-tumor effect was obtained in the administration test in the above-described (1) was collected before the administration of the therapeutic agent for cancer, and 10 days and 30 days after the first administration. Peripheral blood mononuclear cells were isolated according to a conventional method, and by the ELISPOT assay for IFNγ using them, the immune inducibility of each administered recombinant protein was assayed.

[0114] In a 96-well plate manufactured by Millipore (MultiScreen-IP, MAIPS 4510), 100 μL/well of 70% ethanol was placed and the plate was left to stand for 5 minutes, followed by removal of the ethanol by aspiration. The plate was washed with sterile water and 300 μL/well of 200 mM Sodium Bicarbonate (pH8.2) was placed therein. After leaving it to stand for 5 minutes, Sodium Bicarbonate was removed by aspiration, and then the plate was washed. Subsequently, 0.5 μl/well of anti-canine interferon γ monoclonal antibody (manufactured by R&D, clone 142529, MAB781) mixed with 200 mM Sodium Bicarbonate was placed in wells, and the plate was incubated at 37°C overnight to immobilize the primary antibody. After removal of the primary antibody by aspiration, 300 μL/well of a blocking solution (1% BSA-5% sucrose-200 mM Sodium Bicarbonate (pH8.2)) was added to the wells, and the plate was incubated at 4°C overnight to block the plate. After removal of the blocking solution by aspiration, 300 μL/well of 10% fetal calf serum-containing RPMI medium (manufactured by Invitrogen) was placed in the wells, and the plate was left to stand for 5 minutes, followed by removal of the medium by aspiration. Subsequently, 5×10^5 cells/well of the canine peripheral blood mononuclear cells suspended in 10% fetal calf serum-containing RPMI medium were placed in the plate, and 10 μL/well of the canine-derived polypeptide or human-derived polypeptide used in each administration was added thereto, followed by culturing the cells under the conditions of 37°C and 5% CO_2 for 24 hours, to allow immunocytes that might exist in the peripheral blood mononuclear cells to produce interferon γ. After the culture, the medium was removed, and the wells were washed 6 times with a washing solution (0.1% Tween 20-200mM Sodium Bicarbonate (pH8.2)). In each well, 100 μL of rabbit anti-dog polyclonal antibody 1000-fold diluted with the above-described blocking solution was placed, and the plate was incubated at 4°C overnight. After washing the wells 3 times with the above-described washing solution, 100 μL of HRP-labeled anti-rabbit antibody 1000-fold diluted with the above-described blocking solution was placed in each well, and the reaction was allowed to proceed at 37°C for 2 hours. After washing the wells 3 times with the above-described washing solution, the resultant was colored with Konica Immunostain (manufactured by Konica), and the wells were washed with water to stop the reaction. Thereafter, the membrane was dried, and the number of the appeared spots was counted using KS ELISPOT (manufactured by Carl Zeiss, Inc.). As a result, in peripheral blood mononuclear cells sampled before the administration of the polypeptide, no spot was detected. On the other hand, in the canine patient after the administration of the polypeptide, 18 and 87 spots were detected in the peripheral blood mononuclear cells sampled 10 days and 30 days, respectively, after the administration.

[0115] From the above results, it was confirmed that immunocytes which specifically react with the administered recombinant protein and produce interferon γ were induced in the canine patient to which the recombinant protein was administered, and it was thought that the anti-tumor effect described in the above-described (1) was exerted by immunoreactions in which these immunocytes were mainly involved.

Example 4: Induction of CD8-positive T Cells Reactive with Epitopes of CD179b-derived Peptide

(1) Prediction of Peptide Motifs Which Bind to HLA-A0201 and HLA-A24

[0116] Information on the amino acid sequence of the human CD179b protein was obtained from GenBank. For prediction of HLA-A0201 and HLA-A24 binding motifs, the amino acid sequence of the human CD179b protein was analyzed employing a computer-based prediction program using a known BIMAS software (available at http://bimas.dcrt.nih.gov/molbio/hla_bind/). As a result, 8 kinds of peptides shown in SEQ ID NOs:108 to 110 and SEQ ID NOs:113 to 117, which were expected to be capable of binding to the HLA-A0201 molecule; and 5 kinds of peptides shown in SEQ ID NOs:110 to 112, SEQ ID NO: 115 and SEQ ID NO:116, which were expected to be capable of binding to the HLA-A24 molecule; were selected.

(2) Induction of Peptide Epitope-reactive CD8-positive T Cells

[0117] From an HLA-A0201-positive healthy individual, peripheral blood was isolated, and the peripheral blood was overlaid on Lymphocyte separation medium (OrganonpTeknika, Durham, NC), followed by centrifugation thereof at

1,500 rpm at room temperature for 20 minutes. A PBMC-containing fraction was recovered and washed 3 times (or more) with cold phosphate buffer to obtain peripheral blood mononuclear cells (PBMCs). The obtained PBMCs were suspended in 20 ml of AIM-V medium (manufactured by Life Technologies, Inc., Grand Island, NY), and allowed to adhere to a culturing flask (manufactured by Falcon) at 37°C under 5% CO_2 for 2 hours. The cells which were not adhered were used for the preparation of T cells, and the adhered cells were used for the preparation of dendritic cells.

[0118] The adhered cells were cultured in AIM-V medium in the presence of IL-4 (1000 U/ml) and GM-CSF (1000 U/ml). Six days later, the medium was replaced with AIM-V medium supplemented with IL-4 (1000 U/ml), GM-CSF (1000 U/ml), IL-6 (1000 U/ml, Genzyme, Cambridge, MA), IL-1β (10 ng/ml, Genzyme, Cambridge, MA) and TNF-α (10 ng/ml, Genzyme, Cambridge, MA), and the culturing was continued for another 2 days. The obtained population of cells which did not adhere was used as the dendritic cells.

[0119] The prepared dendritic cells were suspended in AIM-V medium at a cell density of 1×10^6 cells/ml, and the peptide shown in SEQ ID NOs:108 to 110 or SEQ ID NOs: 113 to 117, which are sequences selected in the above (1) and expected to be capable of binding to the HLA-A201 molecule, was added to the resulting suspension at a concentration of 10 μg/ml, followed by culture using a 96-well plate under the conditions of 37°C, 5% CO_2 for 4 hours. Thereafter, the cells were irradiated with X-ray (3000 rad), washed with AIM-V medium, suspended in AIM-V medium containing 10% human AB serum (Nabi, Miami, FL), IL-6 (1000 U/ml) and IL-12 (10 ng/ml, Genzyme, Cambridge, MA), and placed in wells of a 24-well plate at a population of 1×10^5 cells/well. The prepared T cell population was added to the wells at a population of 1 x 10^6 cells/well, and the cells were cultured at 37°C under 5% CO_2. Seven days later, each culture supernatant was discarded, and the cells were treated with each of the peptides obtained in the same manner as described above. After irradiation with X-ray, the dendritic cells were suspended in AIM-V medium containing 10% human AB serum (Nabi, Miami, FL), IL-7 (10 U/ml, Genzyme, Cambridge, MA) and IL-2 (10 U/ml, Genzyme, Cambridge, MA) (cell density: 1×10^5cells/ml), and the cells were placed in wells of a 24-well plate at a cell population of 1 x 10^5 cells/well and further cultured. The same operations were repeated 4 to 6 times at intervals of 7 days, and the stimulated T cells were then recovered, after which induction of CD8-positive T cells were confirmed by flow cytometry.

[0120] Also for the peptides shown in SEQ ID NOs:110, 111, 112, 115 and 116, which were expected to be capable of binding to the HLA-A24 molecule, induction of peptide epitope-reactive CD8-positive T cells was attempted using dendritic cells and a T cell population induced from peripheral blood of an HLA-A24-positive healthy individual.

[0121] As a negative control, a peptide outside the scope of the present invention (SEQ ID NO:118) was used.

Example 5: Determination of CD179b-derived Cytotoxic T Cell Antigen Epitopes Which Stimulate HLA-A0201-positive CD8-positive T Cells

(1) IFN-γ-Producing Ability

[0122] In order to examine the specificity of each of the T cells, whose growth was confirmed among the T cells induced as described above, to peptide epitopes, 5×10^3 T cells were added to 5×10^4 T2 cells (Salter RD et al., Immunogenetics, 21:235-246 (1985), purchased from ATCC) which were pulsed with each peptide and expresses the HLA-A0201 molecule (cultured in AIM-V medium supplemented with each peptide at a concentration of 10 μg/ml, at 37°C under 5% CO_2 for 4 hours), and the cells were cultured in AIM-V medium containing 10% human AB serum in a 96-well plate for 24 hours. The supernatant after the culturing was recovered and the production amount of IFN-γ was measured by ELISA. As a result, production of IFN-γ was confirmed in the culture supernatants in the wells of T2 cells pulsed with the peptides of SEQ ID NOs:108 to 110 and SEQ ID NOs: 113 to 117, when compared with the culture supernatants in the wells of T2 cells which were not pulsed with a peptide (Fig. 2). From these results, it was revealed that the above-described peptides are T cell epitope peptides having a capacity to specifically stimulate, and allow proliferation of, the HLA-A0201-positive CD8-positive T cells, thereby inducing production of IFN-γ.

[0123] In Fig. 2, reference numerals 3, 4, 5, 6, 7, 8, 9 and 10 in the abscissa indicate the IFN-γ-producing abilities of the HLA-A0201-positive CD8-positive T cells due to stimulation from the T2 cells pulsed with the peptides of SEQ ID NOs:108, 109, 110, 113, 114, 115, 116 and 117, respectively. Reference numeral 11 indicates the result for the peptide of SEQ ID NO: 118 used as the negative control.

(2) Cytotoxicity Assay

[0124] Subsequently, whether or not the peptides of SEQ ID NOs:108 to 110 and SEQ ID NOs: 113 to 117 used in the present invention are presented on the HLA-A0201 molecules on tumor cells which are HLA-A0201-positive and express CD179b, and whether or not the CD8-positive T cells stimulated by these peptides can damage the tumor cells which are HLA-A0201-positive and express CD179b were examined. In a 50-ml centrifugal tube, 10^6 cells of a B cell leukemia cell line, Namalwa cells (purchased from ATCC), whose expression of CD179b had been confirmed, were collected, and 100 μCi of chromium 51 was added thereto, followed by incubation at 37°C for 2 hours. Thereafter, the

cells were washed 3 times with RPMI medium (manufactured by Gibco) containing 10% fetal calf serum (manufactured by Gibco), and placed in wells of a 96-well V-bottom plate in an amount of 10^3 cells/well. Further, to each well, 5×10^4 T cells suspended in RPMI medium containing 10% fetal bovine serum, which cells were stimulated by each peptide, and HLA-A0201-positive, peptide epitope-reactive and CD8-positive, were added, followed by culture at 37°C under 5% CO_2 for 4 hours. Thereafter, by measuring the amount of chromium 51 in the culture supernatant, which was released from the damaged tumor cells, the cytotoxic activity of the CD8-positive T cells stimulated by each peptide was calculated. As a result, it was revealed that the HLA-A0201-positive CD8-positive T cells stimulated by the peptide have a cytotoxic activity against Namalwa cells (Fig. 3). The CD8-positive T cells induced using the negative control peptide (SEQ ID NO: 118) did not show a cytotoxic activity. Thus, it was proved that each of the peptides used in the present invention (SEQ ID NOs:108 to 110 and SEQ ID NOs:113 to 117) is presented on the HLA-A0201 molecules on tumor cells which are HLA-A0201-positive and express CD179b, and that the peptide has an ability to induce CD8-positive cytotoxic T cells which can damage such tumor cells.

[0125] The cytotoxic activity was determined by, as described above, mixing 10^5 CD8-positive T cells stimulated and induced with each of the peptides used in the present invention and 10^3 cells of the B cell leukemia cell line Namalwa which were made to incorporate chromium 51; culturing the resulting mixture for 4 hours; measuring the amount of chromium 51 released to the culture medium after the culturing; and calculating the cytotoxic activity of the CD8-positive T cells against the Namalwa cells according to the following equation*.

*Equation: Cytotoxic activity (%) = the amount of chromium 51 released from Namalwa cells upon addition of CD8-positive T cells / the amount of chromium 51 released from the target cells upon addition of 1 N hydrochloric acid × 100.

[0126] In Fig. 3, reference numerals 12, 13, 14, 15, 16, 17, 18 and 19 in the abscissa indicate the cytotoxic activities of the HLA-A0201-positive CD8-positive T cells against the Namalwa cells, which T cells were stimulated using SEQ ID NOs:108, 109, 110, 113, 114, 115, 116 and 117, respectively. Reference numeral 20 indicates the cytotoxic activity of CD8-positive T cells induced using the peptide of the negative control (SEQ ID NO: 118).

Example 6: Determination of CD179b-derived Cytotoxic T Cell Antigen Epitopes Which Stimulate HLA-A24-positive CD8-positive T Cells

(1) IFN-γ-Producing Ability

[0127] In order to examine the specificity of the peptide epitope-reactive CD8-positive T cells induced in Example 3(2) to peptide epitopes in the same manner as in Example 5(1), 5×10^3 cells of the above-described T cells were added to 5×10^4 JTK-LCL cells expressing HLA-A24 molecules (purchased from RIKEN), which JTK-LCL cells were pulsed using the peptide of SEQ ID NOs:110, 111, 112, 115 or 116 (cultured in AIM-V medium supplemented with each peptide at a concentration of 10 μg/ml, at 37°C under 5% CO_2 for 4 hours), and the cells were cultured in AIM-V medium containing 10% human AB serum in a 96-well plate for 24 hours. The supernatant after the culturing was recovered and the production amount of IFN-γ was measured by ELISA. As a result, production of IFN-γ was confirmed in the culture supernatants in the wells of JTK-LCL cells pulsed with the peptides of SEQ ID NOs:110, 111, 112, 115 and 116, when compared with the culture supernatants in the wells of JTK-LCL cells which were not pulsed with a peptide (Fig. 4). From these results, it was revealed that the above-described peptides are T cell epitope peptides having a capacity to specifically stimulate, and allow proliferation of, the HLA-A24-positive CD8-positive T cells, thereby inducing production of IFN-γ.

[0128] In Fig. 4, reference numerals 21, 22, 23, 24 and 25 in the abscissa indicate the IFN-γ-producing abilities of the HLA-A24-positive CD8-positive T cells due to stimulation from the JTK-LCL cells pulsed with the peptides of SEQ ID NOs:110, 111, 112, 115 and 116, respectively. Reference numeral 26 indicates the result for the peptide of SEQ ID NO:118 used as the negative control.

(2) Cytotoxicity Assay

[0129] Subsequently, whether or not the peptides of SEQ ID NOs:110, 111, 112, 115 and 116 used in the present invention are presented on the HLA-A24 molecules on cells which are HLA-A24-positive and express CD179b, and whether or not the CD8-positive T cells stimulated by these peptides can damage the tumor cells which are HLA-A24-positive and express CD179b were examined in the same manner as in Example 5(2). In a 50-ml centrifugal tube, 10^6 JTK-LCL cells, which are HLA-A24-positive and express CD179b, were collected, and 100 μCi of chromium 51 was

added thereto, followed by incubation at 37°C for 2 hours. Thereafter, the cells were washed 3 times with RPMI medium containing 10% fetal calf serum, and placed in wells of a 96-well V-bottom plate in an amount of 10^3 cells/well. Further, to each well, 5×10^4 T cells suspended in RPMI medium containing 10% fetal calf serum, which cells were stimulated with each peptide, and HLA-A24-positive, peptide epitope-reactive and CD8-positive, were added, followed by culture at 37°C under 5% CO_2 for 4 hours. Thereafter, by measuring the amount of chromium 51 in the culture supernatant, which was released from the damaged cells, the cytotoxic activity of the CD8-positive T cells stimulated by each peptide was calculated. As a result, it was revealed that the HLA-A24-positive CD8-positive T cells stimulated by the peptide have a cytotoxic activity against JTK-LCL cells (Fig. 5). Thus, it was proved that each of the peptides used in the present invention (SEQ ID NOs:110, 111, 112, 115 and 116) is presented on the HLA-A24 molecules on cells which are HLA-A24-positive and express CD179b, and that the peptide has an ability to induce CD8-positive cytotoxic T cells which can damage such cells. The CD8-positive T cells induced using the negative control peptide (SEQ ID NO: 118) did not show a cytotoxic activity.

[0130] In Fig. 5, reference numerals 27, 28, 29, 30 and 31 indicate the cytotoxic activities of the HLA-A24-positive CD8-positive T cells stimulated with the peptides of SEQ ID NO: 110, 111, 112, 115 and 116, respectively, against JTK-LCL cells. Reference numeral 32 indicates the cytotoxic activity of CD8-positive T cells induced using the peptide of the negative control (SEQ ID NO:118).

Example 7: Detection of Cancer Using Recombinant Protein

(1) Detection of Canine Cancer

[0131] From 153 canine patients whose malignant tumor was confirmed and 264 healthy dogs, blood was collected, and sera were separated therefrom. Using the dog-derived cancer antigen protein prepared in Example 2 (the 5th to 120th amino acids in the amino acid sequence shown in SEQ ID NO:5) and anti-dog IgG antibody, the titer of IgG antibody in the sera which specifically reacts with the polypeptide was measured by ELISA.

[0132] Immobilization of the prepared polypeptide on a solid phase was carried out by placing 100 μL/well of the recombinant protein solution diluted to 100 μg/mL with phosphate-buffered saline in a 96-well Immobilizer Amino plate (manufactured by Nunc), followed by leaving the plate to stand at 4°C overnight. Blocking was carried out by adding 100 μL/well of a solution, which was prepared by dissolving 4 g of Block Ace powder (manufactured by DS Pharma Biomedical Co., Ltd.) into 100 ml of purified water, into the wells, and shaking the plate at room temperature for 1 hour. The serum 1000-fold diluted with the blocking solution was added to the wells in an amount of 100 μL/well, and the plate was shaken at room temperature for 3 hours to allow the reaction to proceed. The wells were washed 3 times with phosphate-buffered saline containing 0.05% Tween 20 (manufactured by Wako Pure Chemical Industries, Ltd.)(hereinafter referred to as PBS-T), and 100 μL/well of HRP-modified dog IgG antibody (Goat anti Dog IgGh+l HRP conjugated: manufactured by BETHYL Laboratories) 3000-fold diluted with the blocking solution was added thereto, followed by shaking the plate at room temperature for 1 hour to allow the reaction to proceed. After washing the wells 3 times with PBS-T, 100 μl/well of an HRP substrate TMB (1-Step Turbo TMB (tetramethylbenzidine), PIERCE) was added, and the enzyme-substrate reaction was allowed to proceed at room temperature for 30 minutes. Thereafter, 100 μl/well of 0.5 M sulfuric acid solution (manufactured by Sigma-Aldrich Japan) was added to the wells to stop the reaction, and the absorbance at 450 nm was measured using a microplate reader. As a control, a case where the same operation was carried out in the same manner as described above except that the prepared recombinant protein was not immobilized, or except that the tumor-bearing dog serum was not reacted, was designed for comparison.

[0133] As the cancer species to be used for the above detection of cancer, 112 samples of breast cancer, 31 samples of lymphoma and 10 samples of leukemia which had been definitely diagnosed as malignant by pathological diagnosis were used.

[0134] These sera derived from the living bodies of the tumor-bearing dogs showed significantly high antibody titers against the recombinant protein. It was revealed that, by diagnosing a sample showing twice the average value of healthy canine samples as malignant, 61 samples (54%) of breast cancer, 21 samples (71%) of lymphoma and 7 samples (70%) of leukemia could be successfully diagnosed as malignant. When the test was similarly carried out using sera from 30 canine patients having a mammary gland tumor which had been definitely diagnosed as benign, the number of samples showing twice the average value of healthy canine samples was 0.

[0135] In the same manner, using the human-derived cancer antigen protein prepared in Example 2 (the amino acid sequence shown in SEQ ID NO:3) and anti-dog IgG antibody, the titer of IgG antibody which specifically reacts with the polypeptide in each of the above-described tumor-bearing dog serum samples was measured by ELISA. As a result, it was revealed that 56 samples (50%) of breast cancer, 18 samples (58%) of lymphoma and 5 samples (50%) of leukemia could be judged as malignant.

[0136] When the detection was carried out in the same manner as described above using pleural effusion and ascites collected from canine patients with terminal cancer, values similar to the results obtained by the detection method using

serum could be detected, and diagnosis of the cancer was possible.

(2) Detection of Human Cancer

[0137] In the same manner, using the human-derived cancer antigen protein (the amino acid sequence shown in SEQ ID NO:3) used in the above detection and anti-human IgG antibody, the titer of IgG antibody in a healthy individual which specifically reacts with the polypeptide was measured. The secondary antibody to be used was an HRP-modified anti-human IgG antibody (manufactured by HRP-Goat Anti-Human IgG(H+L) Conjugate: manufactured by Zymed Laboratories) 10000-diluted with the blocking solution. As a positive control, egg white albumin which was prepared to 50 μg/ml with phosphate-buffered saline and immobilized on the solid phase was used. As a result, in the case of the egg white albumin, seven healthy individuals showed an absorbance of 0.45 at 450 nm on average, which was high. On the other hand, in the case of the above-described polypeptide, the absorbance was 0, which means that the reaction was not detected at all.

[0138] Further, in the same manner as described above, using 17 samples of sera derived from patients suffering from malignant breast cancer (purchased from Promeddx), the titer of IgG antibody in each serum which specifically reacts with the human-derived cancer antigen protein (amino acid sequence shown in SEQ ID NO:3) was similarly measured. As a result, in the case of the above-described polypeptide, the 17 breast cancer patients showed an absorbance of 0.28 at 450 nm on average, which was high. Thus, it was revealed that cancer can be detected by the present method also in human.

INDUSTRIAL APPLICABILITY

[0139] The present invention is useful for therapy of breast cancer and/or leukemia since it provides an immunity-inducing agent containing a polypeptide which exerts an anti-tumor activity against a cancer(s) (tumor(s)) such as breast cancer and/or leukemia. Further, the present invention is useful for diagnosis of breast cancer and/or leukemia since it provides a novel detection method for breast cancer and/or leukemia.

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<213> Canis familiaris

<400> 7

```
Ser Gly Val Pro Asp Arg Phe Ser Thr Ser Arg Ser Gly Tyr Thr Ala
1               5                  10                  15

Thr Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Gly Asp Tyr Tyr
            20                  25                  30

Cys Ser Thr Trp Asp Asn Asp Leu Lys Gly Ser Val Phe Gly Gly Gly
        35                  40                  45

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

Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu
65                  70                  75                  80

Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp
                85                  90                  95

Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro
            100                 105                 110

Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu
        115                 120                 125

Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr
    130                 135                 140

His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
145                 150                 155                 160
```

<210> 8
<211> 634
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(496)
<223>

<400> 8

```
g gac act gaa cgg ccc tct ggg atc cct gac cgc ttc tct ggc tcc agt     49
  Asp Thr Glu Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser
  1               5                  10                  15

tca ggg aac aca cac acc ctg acc atc aga ggg gct cgg gcc gag gac       97
Ser Gly Asn Thr His Thr Leu Thr Ile Arg Gly Ala Arg Ala Glu Asp
```

```
                20                  25                  30

gag gct gac tat tac tgc gag tca gca gtc agt act gat atc ggc gtg      145
Glu Ala Asp Tyr Tyr Cys Glu Ser Ala Val Ser Thr Asp Ile Gly Val
        35                  40                  45

ttc ggc gga ggc acc cac ctg acc gtc ctc ggt cag ccc agg gcc tcc      193
Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Arg Ala Ser
    50                  55                  60

ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc aac      241
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn
65                  70                  75                  80

aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggt gtg      289
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val
                85                  90                  95

acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag      337
Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu
            100                 105                 110

acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc      385
Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
        115                 120                 125

tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc      433
Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser
    130                 135                 140

tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc      481
Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro
145                 150                 155                 160

gca gag tgc tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct      536
Ala Glu Cys Ser

caggacctcc aggaggatct tgcctcccat ctgggtcatc ccgctcttct ccccgcaccc    596

aggcagcact caataaagtg ttctttgttc aatcaaaa                           634
```

<210> 9
<211> 164
<212> PRT
<213> Canis familiaris

<400> 9

```
Asp Thr Glu Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser
1               5                  10                  15

Ser Gly Asn Thr His Thr Leu Thr Ile Arg Gly Ala Arg Ala Glu Asp
            20                  25                  30

Glu Ala Asp Tyr Tyr Cys Glu Ser Ala Val Ser Thr Asp Ile Gly Val
        35                  40                  45

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

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn
65                  70                  75                  80

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

Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu
            100                 105                 110

Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
        115                 120                 125

Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser
    130                 135                 140

Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro
145                 150                 155                 160

Ala Glu Cys Ser
```

<210> 10
<211> 635
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(490)
<223>

<400> 10

```
c cga cct gca ggg gta ccc gat cga ttc tct ggg tcc aag tca ggc ggg      49
  Arg Pro Ala Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly
  1               5                   10                  15

tca gcc atc ctg acc atc tct ggg ctc cag cct gag gac gaa tgt gat      97
Ser Ala Ile Leu Thr Ile Ser Gly Leu Gln Pro Glu Asp Glu Cys Asp
            20                  25                  30

tat tac tgt tcg tct tgg gat aag ggt ctc agc agg tcc gtg ttc ggc     145
Tyr Tyr Cys Ser Ser Trp Asp Lys Gly Leu Ser Arg Ser Val Phe Gly
        35                  40                  45

gga ggc acc cac ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg     193
Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser
    50                  55                  60

gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc     241
Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala
65                  70                  75                  80

acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg     289
Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val
                85                  90                  95

gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag acc acc     337
Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr
            100                 105                 110

aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc tac ctg     385
Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu
        115                 120                 125

agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg     433
Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu
    130                 135                 140

gtc acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc gca gag     481
Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu
145                 150                 155                 160

tgc tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct             530
Cys Ser

caggacctcc aggaggatct tgcctcccat ctgggtcatc ccgcccttct ccccgcaccc   590

aggcagcact caataaagtg ttctttgttc aatcagaaaa aaaaa                   635
```

<210> 11

<211> 162

<212> PRT

<213> Canis familiaris

<400> 11

```
Arg Pro Ala Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly
1               5                  10                  15

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

Tyr Tyr Cys Ser Ser Trp Asp Lys Gly Leu Ser Arg Ser Val Phe Gly
        35                  40                  45

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

Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala
65                  70                  75                  80

Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val
                85                  90                  95

Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr
            100                 105                 110

Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu
        115                 120                 125

Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu
    130                 135                 140

Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu
145                 150                 155                 160

Cys Ser
```

<210> 12
<211> 583
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(445)
<223>

<400> 12

```
c aaa gcc gcc ctc acc atc aca gga gcc cag cct gag gac gag gct gac      49
  Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln Pro Glu Asp Glu Ala Asp
  1               5                  10                  15

tac tac tgt gct ctg gga tta agt agt agt agt agc cat agt gtg ttc      97
Tyr Tyr Cys Ala Leu Gly Leu Ser Ser Ser Ser Ser His Ser Val Phe
            20                  25                  30

ggc gga ggc acc cat ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc     145
Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro
        35                  40                  45

tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag     193
Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys
    50                  55                  60

gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agt ggc gtg acg     241
Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr
65                  70                  75                  80

gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag acc     289
Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr
                85                  90                  95

acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc tac     337
Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr
            100                 105                 110

ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc tgc     385
Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys
        115                 120                 125

ctg gtc aca cac gag ggg agc acc gtg gag aag aag gtg gcc ccc gca     433
Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala
    130                 135                 140

gag tgc tct tag gttcccgacg cccccgccca cctaaggggg cccggagcct         485
Glu Cys Ser
145

caggacctcc aggaggatct tgcctcctat ctgggtcatc ccgcccttct ccccacaccc   545

aggcagcact caataaagtg ttctttgttc aatcagaa                           583
```

<210> 13
<211> 147
<212> PRT
<213> Canis familiaris

<400> 13

```
Lys Ala Ala Leu Thr Ile Thr Gly Ala Gln Pro Glu Asp Glu Ala Asp
1               5                  10                  15

Tyr Tyr Cys Ala Leu Gly Leu Ser Ser Ser Ser Ser His Ser Val Phe
            20                  25                  30

Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro
        35                  40                  45
```

```
Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys
 50                  55                  60

Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr
65                  70                  75                  80

Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr
                85                  90                  95

Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr
            100                 105                 110

Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys
        115                 120                 125

Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala
 130                 135                 140

Glu Cys Ser
145
```

<210> 14
<211> 796
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(643)
<223>

<400> 14

```
g ctg act cag ccg gcc tca gtg tct ggg tcc ctg ggc cag agg atc acc      49
  Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Leu Gly Gln Arg Ile Thr
  1               5                  10                  15

atc tcc tgc act gga agc agc tcc aac att gga ggt aat aat gtg ggt      97
Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Gly Asn Asn Val Gly
            20                  25                  30

tgg tac cag cag ctc cca gga aga ggc ccc aga act gtc atc ttt act     145
Trp Tyr Gln Gln Leu Pro Gly Arg Gly Pro Arg Thr Val Ile Phe Thr
        35                  40                  45

aca cat agt cga ccc tcg ggg gtg tcc gat cga ttc tct gcc tcc aag     193
Thr His Ser Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Ala Ser Lys
    50                  55                  60

tct ggc agc aca gcc acc ctg acc atc tct ggg ctc cag gct gag gat     241
Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
65                  70                  75                  80

gag gct gat tat tac tgc tca acg tgg gat gat agt ctc agt gct gct     289
Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Asp Ser Leu Ser Ala Ala
                85                  90                  95

gtg ttc ggc gga ggc acc cac ctg acc gtc ctc ggt cag ccc aag gcc     337
Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110

tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc     385
Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala
        115                 120                 125


aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc     433
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly
    130                 135                 140

gtg acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg     481
Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val
145                 150                 155                 160

gag acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc     529
Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175

agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc     577
Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe
            180                 185                 190

agc tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg gcc     625
Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala
        195                 200                 205

ccc gca gag tgc tct tag gttcccgacg gccccgccca ccgaaggggg            673
Pro Ala Glu Cys Ser
    210

cccggagcct caggacctcc aggaggatct tgcctcccat ctgggtcatc ccgcccttct   733

ccccgcaccc aggcagcact caataaagtg ttctttgttc aatcaaaaaa aaaaaaaaaa   793

aaa                                                                 796
```

<210> 15
<211> 213
<212> PRT
<213> Canis familiaris

<400> 15

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

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

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

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

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

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

Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110

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

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

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

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

Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe
            180                 185                 190

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

Pro Ala Glu Cys Ser
    210
```

<210> 16
<211> 1306
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(646)
<223>

<400> 16

```
c tcc tat gtg ctg aca cag ctg cca tcc atg act gtg acc ctg aag cag      49
  Ser Tyr Val Leu Thr Gln Leu Pro Ser Met Thr Val Thr Leu Lys Gln
  1               5                  10                  15

acg gcc cgc atc acc tgt gag gga gac agc att gga agc aaa aga gtt      97
Thr Ala Arg Ile Thr Cys Glu Gly Asp Ser Ile Gly Ser Lys Arg Val
            20                  25                  30

tac tgg tac caa cag aac ctg ggc cag gtc cct cta ctg att atc tat     145
Tyr Trp Tyr Gln Gln Asn Leu Gly Gln Val Pro Leu Leu Ile Ile Tyr
        35                  40                  45

gat gat gcc acc agg ccg tca agg atc cct gac cga ttc tcc ggc gcc     193
Asp Asp Ala Thr Arg Pro Ser Arg Ile Pro Asp Arg Phe Ser Gly Ala
    50                  55                  60

aac tcg ggg gac aca gcc acc ctg acc atc agc ggg gcc ctg gcc gag     241
Asn Ser Gly Asp Thr Ala Thr Leu Thr Ile Ser Gly Ala Leu Ala Glu
65                  70                  75                  80

gac gag gct gac tat tac tgt cag gtg tgg gac agt gat agt aag act     289
Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp Ser Lys Thr
                85                  90                  95

ggt gta ttc ggc gga ggc acc cac ctg acc gtc ctc ggt cag ccc aag     337
Gly Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys
            100                 105                 110

gcc tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc     385
Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly
        115                 120                 125

gcc aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc     433
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser
```

```
        130                 135                 140

ggt gtg acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc      481
Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly
145                 150                 155                 160

gtg gag acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc      529
Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
                165                 170                 175

agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc      577
Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser
            180                 185                 190

ttc agc tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg      625
Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val
        195                 200                 205

gcc ccc gca gag tgc tct tag gttcccgacg gccccgccca ccgaaggggg         676
Ala Pro Ala Glu Cys Ser
    210

cccggagcct caggacctcc aggaggatct tgcctcccat ctgggtcatc ccgctcttct    736

ccccgcaccc aggcagcact caataaagtg ttctttgttc aatcagaaaa aaaaaaaaaa    796

aaaaaactcg agccggctgg agtctgggat gcagaacatg agcatccata cgaagacgac    856

cagcggctac tccggtggcc tgaacttggc ctacgggggc ctcacgagcc ccggcctcaa    916

ctacggccag agctccttcc agtccggctt tggccctggc ggttccttca gccgcagcag    976

ctcctccaag gccgtggttg tgaagaagat cgagactcgc gatgggaagc tggtgtctga   1036

gtcgtctgac gtcctgccca agtgaacggc cagcgcgggc ccccccagcc tccttgctct   1096

tgtggcccca tgaagccttc gggggaagga gctgtgcagg ggagcctcgc gtacgagaga   1156

cccgcctaag gctcagcccc ggtccccagc ctacccttag ggggagtcta ctgccctggg   1216

taccccttct tgtccgtgcc cccgaccgaa agccaattca agtgtctttt cccaaataaa   1276

gccgctgcca gtcccaaaaa aaaaaaaaaa                                    1306
```

<210> 17
<211> 214
<212> PRT
<213> Canis familiaris

<400> 17

```
Ser Tyr Val Leu Thr Gln Leu Pro Ser Met Thr Val Thr Leu Lys Gln
1               5                  10                  15

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

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

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

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

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp Ser Lys Thr
                85                  90                  95

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

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

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

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

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

Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser
            180                 185                 190

Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val
        195                 200                 205

Ala Pro Ala Glu Cys Ser
    210
```

<210> 18
<211> 859
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(718)
<223>

<400> 18

```
g acc tcc aac atg gcc tgg tcc cct ctc ctc ctc aca ctc ctt gct tcc      49
  Thr Ser Asn Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Ala Ser
  1               5                  10                  15

tgc aca gga tcc tgg gcc cag tct gtg cta act cag ccg acc tcg gtg      97
Cys Thr Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Thr Ser Val
            20                  25                  30

tcg ggg tcc ctt ggc cag agg gtc acc atc tcc tgc tct ggc agc tcg     145
Ser Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser
        35                  40                  45

acc aac atc ggt tct gtt ggt gcg act tgg tac caa cac ctc cca gga     193
Thr Asn Ile Gly Ser Val Gly Ala Thr Trp Tyr Gln His Leu Pro Gly
    50                  55                  60

aag gcc cct aga ctc ctc ctc tac aca cat ggg gaa cgg ccg tca ggg     241
Lys Ala Pro Arg Leu Leu Leu Tyr Thr His Gly Glu Arg Pro Ser Gly
65                  70                  75                  80

atc cct gac cgg ttt tcc ggc tcc gag tct gcc aac tcg gac acc ctg     289

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

acc atc act gga ctt cag gct gag gac gag gct gat tac tac tgc cag     337
Thr Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
            100                 105                 110

tcc ttt gat agc acg ctt gag act gct gtg ttc ggc ggc ggc act cac     385
Ser Phe Asp Ser Thr Leu Glu Thr Ala Val Phe Gly Gly Gly Thr His
        115                 120                 125

ctg acc gtc ctt ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc     433
Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
    130                 135                 140

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc     481
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
145                 150                 155                 160

ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca     529
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
                165                 170                 175

gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag     577
Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
            180                 185                 190

cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct     625
Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
        195                 200                 205

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag     673
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
    210                 215                 220

ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag          718
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct    778

tgcctcccat ctgggtcatc ccgctcttct ccccgcaccc aggcagcact caataaagtg    838

ttctttgttc aatcagaaaa a                                              859
```

<210> 19
<211> 238
<212> PRT
<213> Canis familiaris

<400> 19

```
Thr Ser Asn Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Ala Ser
1               5                  10                  15

Cys Thr Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Thr Ser Val
            20                  25                  30

Ser Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser
        35                  40                  45

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

Lys Ala Pro Arg Leu Leu Leu Tyr Thr His Gly Glu Arg Pro Ser Gly

65                  70                  75                  80

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

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

Ser Phe Asp Ser Thr Leu Glu Thr Ala Val Phe Gly Gly Gly Thr His
        115                 120                 125

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

Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
145                 150                 155                 160

Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
                165                 170                 175

Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
            180                 185                 190

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
        195                 200                 205

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
    210                 215                 220

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235
```

<210> 20
<211> 875
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(715)
<223>

<400> 20

```
c tcc aac atg gcc tgg tcc cct ctc ctc ctc aca ctc ctt gtt tac tgc     49
  Ser Asn Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Val Tyr Cys
  1               5                  10                  15

aca ggg tcc tgg gcc cag tct gta ctg act cat ccg acc tca gtg tcg      97
Thr Gly Ser Trp Ala Gln Ser Val Leu Thr His Pro Thr Ser Val Ser
            20                  25                  30

ggg tcc ctt ggc cag agg gtc acc att tcc tgc tcc gga agc acg aac     145
Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Asn
        35                  40                  45

aac atc ggt act gtt ggt gcg ggc tgg tac caa cag ttc cca gga aag     193
Asn Ile Gly Thr Val Gly Ala Gly Trp Tyr Gln Gln Phe Pro Gly Lys
    50                  55                  60
```

```
gcc cct aaa ctc ctc att tac agt gat ggg aat cga ccg tca ggg gtc      241
Ala Pro Lys Leu Leu Ile Tyr Ser Asp Gly Asn Arg Pro Ser Gly Val
65                  70                  75                  80

cct gac cgg ttt tcc ggc tcc aag tca ggc aac tca gcc acc ctg acc      289
Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Ser Ala Thr Leu Thr
                85                  90                  95

atc att gga ctt cag gct gag gac gag gct gat tac tac tgt cag tct      337
Ile Ile Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
            100                 105                 110

gtt gat ccc acg ctt ggt ggt cat gtg ttc ggc gga ggc acc cat ctg      385
Val Asp Pro Thr Leu Gly Gly His Val Phe Gly Gly Gly Thr His Leu
        115                 120                 125

acc gtc ctc ggt cag ccc aag gcc tcc cct tcg gtc aca ctc ttc ccg      433
Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro
    130                 135                 140

ccc tcc tct gag gag ctt ggc gcc aac aag gcc acc ctg gtg tgc ctc      481
Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
145                 150                 155                 160

atc agc gac ttc tac ccc agc ggc gtg aca gtg gcc tgg aag gca gac      529
Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp
                165                 170                 175

ggc agc ccc atc acc cag ggt gtg gag acc acc aag ccc tcc aag cag      577
Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
            180                 185                 190

agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac      625
Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
        195                 200                 205

aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag ggg      673
Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly
    210                 215                 220

agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag              715
Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235

gttcctgatg tcccccgccc accaaagggg gctcagagcc tcaggacctc caggaggatc    775

ttgcctccca tctgggtcat cccagccttt ccccttaaac ccaggcaaca ttcaataaag    835

tgttctttct tcaatcagaa aaaaaaaaaa aaaaaaaaaa                          875
```

<210> 21

<211> 237

<212> PRT

<213> Canis familiaris

<400> 21

```
Ser Asn Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Val Tyr Cys
1               5                  10                  15

Thr Gly Ser Trp Ala Gln Ser Val Leu Thr His Pro Thr Ser Val Ser
            20                  25                  30

Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Asn
        35                  40                  45

Asn Ile Gly Thr Val Gly Ala Gly Trp Tyr Gln Gln Phe Pro Gly Lys
    50                  55                  60

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

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

Ile Ile Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
            100                 105                 110

Val Asp Pro Thr Leu Gly Gly His Val Phe Gly Gly Gly Thr His Leu
        115                 120                 125

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

Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
145                 150                 155                 160

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

Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
            180                 185                 190

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
        195                 200                 205

Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly
    210                 215                 220

Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235
```

<210> 22
<211> 862
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (2)..(721)
<223>

<400> 22

```
g atg atc ttc acc atg gcc tgg tcc cct ctc ctc ctc ggc ctc ctt gct     49
  Met Ile Phe Thr Met Ala Trp Ser Pro Leu Leu Leu Gly Leu Leu Ala
  1               5                  10                  15

cac tgc aca ggg tcc tgg gcc cag tct atg ctg act cag ccg gcc tca       97
His Cys Thr Gly Ser Trp Ala Gln Ser Met Leu Thr Gln Pro Ala Ser
            20                  25                  30

gtg tct ggg tcc ctg ggc cag aag gtc acc atc tcc tgc act gga agc      145
Val Ser Gly Ser Leu Gly Gln Lys Val Thr Ile Ser Cys Thr Gly Ser
        35                  40                  45
```

```
agc tcc aac atc ggt gct tat tat gtg agc tgg tac caa cag tcc cca      193
Ser Ser Asn Ile Gly Ala Tyr Tyr Val Ser Trp Tyr Gln Gln Ser Pro
    50                  55                  60

gga aaa ggc cct aga acc gtc atc tat ggt gat aat tac cga cct tca      241
Gly Lys Gly Pro Arg Thr Val Ile Tyr Gly Asp Asn Tyr Arg Pro Ser
65                  70                  75                  80

ggg gtc ccc gat cga ttc tct ggc tcc aag tca ggc agt tca gcc acc      289
Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Ser Ser Ala Thr
                85                  90                  95

ctg acc atc tct ggg ctc cag gct gag gac gag gct gaa tat tac tgc      337
Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys
            100                 105                 110

tta tca tgg gat aat agt ctc aga ggt ggt gtg ttc ggc gga ggc acc      385
Leu Ser Trp Asp Asn Ser Leu Arg Gly Gly Val Phe Gly Gly Gly Thr
        115                 120                 125

cac ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc      433
His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu
    130                 135                 140

ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg      481
Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val
145                 150                 155                 160

tgc ctc atc agc gac ttc tac ccc agc ggt gtg acg gtg gcc tgg aag      529
Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys
                165                 170                 175

gca gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc      577
Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser
            180                 185                 190

aag cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg      625
Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr
        195                 200                 205

cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac      673
Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His
    210                 215                 220

gag ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag      721
Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct    781

tgcctcccat ctgggtcatc ccgctcttct ccccgcaccc aggcagcact caataaagtg    841

ttctttgttc aatcagaaaa a                                              862
```

<210> 23

<211> 239

<212> PRT

<213> Canis familiaris

<400> 23

```
Met Ile Phe Thr Met Ala Trp Ser Pro Leu Leu Leu Gly Leu Leu Ala
1               5                  10                  15

His Cys Thr Gly Ser Trp Ala Gln Ser Met Leu Thr Gln Pro Ala Ser
            20                  25                  30

Val Ser Gly Ser Leu Gly Gln Lys Val Thr Ile Ser Cys Thr Gly Ser
        35                  40                  45

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

Gly Lys Gly Pro Arg Thr Val Ile Tyr Gly Asp Asn Tyr Arg Pro Ser
65                  70                  75                  80

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

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

Leu Ser Trp Asp Asn Ser Leu Arg Gly Gly Val Phe Gly Gly Gly Thr
        115                 120                 125

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

Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val
145                 150                 155                 160

Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys
                165                 170                 175

Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser
            180                 185                 190

Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr
        195                 200                 205

Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His
    210                 215                 220

Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235
```

<210> 24
<211> 884
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (2)..(736)
<223>

<400> 24

```
g aag aca gga tcc gtg atg acc tcc acc atg gga tgg ttc cct ctg ctc     49
  Lys Thr Gly Ser Val Met Thr Ser Thr Met Gly Trp Phe Pro Leu Leu
  1               5                  10                  15

ctc acc ctc ctg gct cac tgc aca ggt tcc tgg gcc cag tct gtg ctg      97
Leu Thr Leu Leu Ala His Cys Thr Gly Ser Trp Ala Gln Ser Val Leu
```

```
                20                  25                  30

act cag ccg gcc tca gtg tct ggg tcc ctg ggc cag agg gtc acc atc      145
Thr Gln Pro Ala Ser Val Ser Gly Ser Leu Gly Gln Arg Val Thr Ile
        35                  40                  45

tcc tgc act gga acc agc tcc aat atc ggt aca gat tat gtg ggc tgg      193
Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Asp Tyr Val Gly Trp
    50                  55                  60

tac caa cag ctc cca gga aga ggc ccc aga acc ctc atc tct gat act      241
Tyr Gln Gln Leu Pro Gly Arg Gly Pro Arg Thr Leu Ile Ser Asp Thr
65                  70                  75                  80

agt cgc cga ccc tcg ggg gtc cct gat cga ttc tct ggc tcc agg tca      289
Ser Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser
                85                  90                  95

ggc acc aca gca atc ctg act atc tct ggg ctc cag gct gag gac gag      337
Gly Thr Thr Ala Ile Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu
            100                 105                 110

gct gat tat tac tgc tca gca tat gac agc agt ctc ggt gga act atc      385
Ala Asp Tyr Tyr Cys Ser Ala Tyr Asp Ser Ser Leu Gly Gly Thr Ile
        115                 120                 125

ttc ggc gga ggc act ttc ctg acc gtc ctc ggt cag ccc aag gcc tcc      433
Phe Gly Gly Gly Thr Phe Leu Thr Val Leu Gly Gln Pro Lys Ala Ser
    130                 135                 140

ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc aac      481
Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn
145                 150                 155                 160

aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc gtg      529
Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val
                165                 170                 175

acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag      577
Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu
            180                 185                 190

acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc      625
Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
        195                 200                 205

tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc      673
Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser
    210                 215                 220

tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc      721
Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro
225                 230                 235                 240

gca gag tgc tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct      776
Ala Glu Cys Ser

caggacctcc aggaggatct tgcctcccat ctgggtcatc ccgcccttct ccccgcaccc    836

aggcagcact caataaagtg ttctttgttc aatcaaaaaa aaaaaaaa                884
```

<210> 25
<211> 244
<212> PRT
<213> Canis familiaris

<400> 25

```
Lys Thr Gly Ser Val Met Thr Ser Thr Met Gly Trp Phe Pro Leu Leu
1               5                  10                  15

Leu Thr Leu Leu Ala His Cys Thr Gly Ser Trp Ala Gln Ser Val Leu
            20                  25                  30

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

Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Asp Tyr Val Gly Trp
    50                  55                  60

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

Ser Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser
                85                  90                  95

Gly Thr Thr Ala Ile Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu
            100                 105                 110

Ala Asp Tyr Tyr Cys Ser Ala Tyr Asp Ser Ser Leu Gly Gly Thr Ile
        115                 120                 125

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

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn
145                 150                 155                 160

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val
                165                 170                 175

Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu
            180                 185                 190

Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
        195                 200                 205

Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser
    210                 215                 220

Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro
225                 230                 235                 240

Ala Glu Cys Ser
```

<210> 26
<211> 729
<212> DNA

<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(574)
<223>

<400> 26

```
c tcc aac att gga ggt aat cat gta ggt tgg tac caa caa ttt cca gga      49
  Ser Asn Ile Gly Gly Asn His Val Gly Trp Tyr Gln Gln Phe Pro Gly
  1               5                  10                  15

aga ggc ccc aga act gtc atc tat agc aca aat gtt cga ccc tcg ggg      97
Arg Gly Pro Arg Thr Val Ile Tyr Ser Thr Asn Val Arg Pro Ser Gly
            20                  25                  30

gtg ccc gat cga ttc tct ggc tcc aag tct gac aac aca ggc acc ctg     145
Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Asp Asn Thr Gly Thr Leu
        35                  40                  45

acc atc tct gga ctc cag gct gag gat gag gct gat tat tat tgc gca     193
Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala
    50                  55                  60

acg tgg gat gat agt ctc agt gtt tct ctg ttc ggc gga ggc acc cac     241
Thr Trp Asp Asp Ser Leu Ser Val Ser Leu Phe Gly Gly Gly Thr His
65                  70                  75                  80

ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc     289
Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
                85                  90                  95

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc     337
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
            100                 105                 110

ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca     385
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
        115                 120                 125

gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag     433
Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
    130                 135                 140

cag acc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct     481
Gln Thr Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
145                 150                 155                 160

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag     529
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
                165                 170                 175

ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag         574
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
            180                 185                 190

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct    634

tgcctcccat ctgggtcatc ccgcccttct ccccgcaccc aggcagcact caataaagtg    694

ttctttgttc aatcagaaaa aaaaaaaaaa aaaaa                               729
```

<210> 27
<211> 190

<212> PRT
<213> Canis familiaris

<400> 27

```
Ser Asn Ile Gly Gly Asn His Val Gly Trp Tyr Gln Gln Phe Pro Gly
1               5                  10                  15

Arg Gly Pro Arg Thr Val Ile Tyr Ser Thr Asn Val Arg Pro Ser Gly
            20                  25                  30

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Asp Asn Thr Gly Thr Leu
        35                  40                  45

Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala
    50                  55                  60

Thr Trp Asp Asp Ser Leu Ser Val Ser Leu Phe Gly Gly Gly Thr His
65                  70                  75                  80

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

Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
            100                 105                 110

Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
        115                 120                 125

Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
    130                 135                 140

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

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
                165                 170                 175

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
            180                 185                 190
```

<210> 28
<211> 1176
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(730)
<223>

<400> 28

```
a gga tcc gtg atg acc tcc acc atg ggc tgg tcc cct ctc atc ctc acc     49
  Gly Ser Val Met Thr Ser Thr Met Gly Trp Ser Pro Leu Ile Leu Thr
  1               5                  10                  15

ctc ttc gct cac tgc gca ggg tcc tgg gcc cag tct gtc ctg act cag       97
Leu Phe Ala His Cys Ala Gly Ser Trp Ala Gln Ser Val Leu Thr Gln
            20                  25                  30

ccg gcc tca gtg tct ggg tcc ctg ggc cag agg gtc acc atc tcc tgc      145
Pro Ala Ser Val Ser Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys
        35                  40                  45

act gga agc agc tcc aat gtt ggt ttt ggc gat tat gtg ggc tgg tac      193
Thr Gly Ser Ser Ser Asn Val Gly Phe Gly Asp Tyr Val Gly Trp Tyr
```

```
     50                  55                  60

cag cag ctc cca gga aga ggc ccc aga acc ctc ttc tac cgt gct act      241
Gln Gln Leu Pro Gly Arg Gly Pro Arg Thr Leu Phe Tyr Arg Ala Thr
65                  70                  75                  80

ggc cga ccc tcg ggg gtc cct gat cga ttc tct gcc tcc agg tca ggc      289
Gly Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Ala Ser Arg Ser Gly
                85                  90                  95

acc aca gcg acc ctg acc atc tct gga ctc cag cct gag gat gaa gcc      337
Thr Thr Ala Thr Leu Thr Ile Ser Gly Leu Gln Pro Glu Asp Glu Ala
            100                 105                 110

gat tat tac tgc tca tcc tat gac tct act ctc ttt tct gtg ttc ggc      385
Asp Tyr Tyr Cys Ser Ser Tyr Asp Ser Thr Leu Phe Ser Val Phe Gly
        115                 120                 125

gga ggc acc tac ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg      433
Gly Gly Thr Tyr Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser
    130                 135                 140

gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc      481
Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala
145                 150                 155                 160

acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg      529
Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val
                165                 170                 175

gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag acc acc      577
Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr
            180                 185                 190

aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc tac ctg      625
Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu
        195                 200                 205

agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg      673
Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu
    210                 215                 220

gtc acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc gca gag      721
Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu
225                 230                 235                 240

tgc tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct              770
Cys Ser

caggacctcc aggaggatct tgcctcccat ctgggtcatc ccgcccttct ccccgcaccc    830

aggcagcact caataaagtg ttccaatttc aagcgactta aatgcatatg gttttttttt    890

tttgatgtga tacagctgtg tttacttcaa cctccaggga atcctaaggg cccagagact    950

ccccttgtgc tgtaagattg tgtccctgaa acaagtcacc tccagccttc cagaggggtg   1010

ggctgcctgg aggcagtggc acgggcctgg gctctctaga atgtgtactg agcaggggca   1070

ggaggcccaa agggccaccc atgcctccag gagcctccgc aggagggagc agagtctgta   1130

gaggctcacg gagaggctgg aagatcactg gaacagcagc aagcca                  1176
```

<210> 29
<211> 242
<212> PRT

<213> Canis familiaris

<400> 29

```
Gly Ser Val Met Thr Ser Thr Met Gly Trp Ser Pro Leu Ile Leu Thr
1               5                  10                  15

Leu Phe Ala His Cys Ala Gly Ser Trp Ala Gln Ser Val Leu Thr Gln
            20                  25                  30

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

Thr Gly Ser Ser Ser Asn Val Gly Phe Gly Asp Tyr Val Gly Trp Tyr
    50                  55                  60

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

Gly Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Ala Ser Arg Ser Gly
                85                  90                  95

Thr Thr Ala Thr Leu Thr Ile Ser Gly Leu Gln Pro Glu Asp Glu Ala
            100                 105                 110

Asp Tyr Tyr Cys Ser Ser Tyr Asp Ser Thr Leu Phe Ser Val Phe Gly
        115                 120                 125

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

Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala
145                 150                 155                 160

Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val
                165                 170                 175

Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr
            180                 185                 190

Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu
        195                 200                 205

Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu
    210                 215                 220

Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu
225                 230                 235                 240

Cys Ser
```

<210> 30

<211> 762
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(609)
<223>

<400> 30

```
ggc cag agg gtc acc atc tcc tgc act gga agc ccc aat gtt ggt tat      48
Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Pro Asn Val Gly Tyr
1               5                  10                  15

ggc aat tac gtg ggc tgg tac cag cag ctc cca gga aca ggc ccc aga      96
Gly Asn Tyr Val Gly Trp Tyr Gln Gln Leu Pro Gly Thr Gly Pro Arg
            20                  25                  30

acc ctc att tat ggt aag aat cac cga ccc gcg ggg gtc cct gat cga     144
Thr Leu Ile Tyr Gly Lys Asn His Arg Pro Ala Gly Val Pro Asp Arg
        35                  40                  45

ttc tct ggc tcc act tca ggc agt tca gcc aca ctg acc atc tct ggg     192
Phe Ser Gly Ser Thr Ser Gly Ser Ser Ala Thr Leu Thr Ile Ser Gly
    50                  55                  60

ctc cag gct gag gat gaa gca gat tat tac tgc tca tcc tat gac atc     240
Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile
65                  70                  75                  80

agt ctc ggt ggt gtt gtg ttc ggc gga ggc acc cat ctg acc gtc ctc     288
Ser Leu Gly Gly Val Val Phe Gly Gly Gly Thr His Leu Thr Val Leu
                85                  90                  95

ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct     336
Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
            100                 105                 110

gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc atc agc gac     384
Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
        115                 120                 125

ttc tac ccc agt ggc gtg acg gtg gcc tgg aag gca gac ggc agc ccc     432
Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
    130                 135                 140

gtc acc cag ggc gtg gag acc acc aag ccc tcc aag cag agc aac aac     480
Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
145                 150                 155                 160

aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa     528
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
                165                 170                 175

tct cac agc agc ttc agc tgc ctg gtc aca cac gag ggg agc acc gtg     576
Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val
            180                 185                 190

gag aag aag gtg gcc ccc gca gag tgc tct tag gttcccgacg cccccgccca    629
Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200

cctaaggggg cccggagcct caggacctcc aggaggatct tgcctcctat ctgggtcatc    689

ccgcccttct ccccacaccc aggcagcact caataaagtg ttctttgttc aatcagaaaa    749

aaaaaaaaaa aaa                                                      762
```

<210> 31
<211> 202
<212> PRT
<213> Canis familiaris

<400> 31

```
Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Pro Asn Val Gly Tyr
1               5                  10                  15

Gly Asn Tyr Val Gly Trp Tyr Gln Gln Leu Pro Gly Thr Gly Pro Arg
            20                  25                  30

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

Phe Ser Gly Ser Thr Ser Gly Ser Ser Ala Thr Leu Thr Ile Ser Gly
    50                  55                  60

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile
65                  70                  75                  80

Ser Leu Gly Gly Val Val Phe Gly Gly Gly Thr His Leu Thr Val Leu
                85                  90                  95

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

Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
        115                 120                 125

Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
    130                 135                 140

Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
145                 150                 155                 160

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
                165                 170                 175

Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val
            180                 185                 190

Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200
```

<210> 32
<211> 826
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(678)
<223>

<400> 32

```
ctt gtc agc ctc ctg gct ctc tgc aca ggt tct gtg gcc tcc tat gtg       48
Leu Val Ser Leu Leu Ala Leu Cys Thr Gly Ser Val Ala Ser Tyr Val
1               5                  10                  15

ctg aca cag ccg ccg tcc atg agt gtg acc ctg agg cag acg gcc cgc       96
Leu Thr Gln Pro Pro Ser Met Ser Val Thr Leu Arg Gln Thr Ala Arg
            20                  25                  30

atc acc tgt gag gga gac agc att gga gat aaa aga gtt tac tgg tac      144
Ile Thr Cys Glu Gly Asp Ser Ile Gly Asp Lys Arg Val Tyr Trp Tyr
        35                  40                  45

cag cag aaa ctg ggc cgg ggc ccg atg ttg att att tat gat ggt acc      192
Gln Gln Lys Leu Gly Arg Gly Pro Met Leu Ile Ile Tyr Asp Gly Thr
    50                  55                  60

tac agg ccg tca ggg atc cct gac cga ttc ttc ggc gcc aat tcg ggg      240
Tyr Arg Pro Ser Gly Ile Pro Asp Arg Phe Phe Gly Ala Asn Ser Gly
65                  70                  75                  80

agc aca gcc acc ctg acc atc agc ggg gcc ctg gcc gag gac gag gct      288
Ser Thr Ala Thr Leu Thr Ile Ser Gly Ala Leu Ala Glu Asp Glu Ala
                85                  90                  95

gac tat tac tgc cag gtg tgg gac aat ggt gaa att att ttc ggc gga      336
Asp Tyr Tyr Cys Gln Val Trp Asp Asn Gly Glu Ile Ile Phe Gly Gly
            100                 105                 110

ggc acc cgt ctg acc gtc ctc ggt cag ccc aag gcc tcc cct tcg gtc      384
Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val
        115                 120                 125

aca ctc ttc ccg ccc tcc tct gag gag ctt ggc gcc aac aag gcc acc      432
Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr
    130                 135                 140

ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc gtg aca gtg gcc      480
Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala
145                 150                 155                 160

tgg aag gca gac ggc agc ccc atc acc cag ggt gtg gag acc acc aag      528
Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys
                165                 170                 175

ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc tac ctg agc      576
Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser
            180                 185                 190

ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc      624
Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val
        195                 200                 205

acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc      672
Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys
    210                 215                 220

tct tag gttcctgatg tcccccgccc accaaagggg gctcagagcc tcaggacctc      728
Ser
225

caggaggatc ttgcctccca tctgggtcat cccagccttt ccccttaaac ccaggcaaca    788

ttcaataaag tgttctttct tcaatcagaa ggggcccg                            826
```

<210> 33
<211> 225

<212> PRT
<213> Canis familiaris

<400> 33

```
Leu Val Ser Leu Leu Ala Leu Cys Thr Gly Ser Val Ala Ser Tyr Val
1               5                  10                  15

Leu Thr Gln Pro Pro Ser Met Ser Val Thr Leu Arg Gln Thr Ala Arg
            20                  25                  30

Ile Thr Cys Glu Gly Asp Ser Ile Gly Asp Lys Arg Val Tyr Trp Tyr
        35                  40                  45

Gln Gln Lys Leu Gly Arg Gly Pro Met Leu Ile Ile Tyr Asp Gly Thr
    50                  55                  60

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

Ser Thr Ala Thr Leu Thr Ile Ser Gly Ala Leu Ala Glu Asp Glu Ala
                85                  90                  95

Asp Tyr Tyr Cys Gln Val Trp Asp Asn Gly Glu Ile Ile Phe Gly Gly
            100                 105                 110

Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val
        115                 120                 125

Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr
    130                 135                 140

Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala
145                 150                 155                 160

Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys
                165                 170                 175

Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser
            180                 185                 190

Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val
        195                 200                 205

Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys
    210                 215                 220

Ser
225
```

<210> 34
<211> 796
<212> DNA

<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(643)
<223>

<400> 34

g ctg act cag ccg gcc tca gtg tct ggg tcc ctg ggc cag agg gtc acc 49

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

atc tcc tgc act gga agc agt tcc aac att gga agt aat gat gtg ggt      97
Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ser Asn Asp Val Gly
            20                  25                  30

tgg tac cag cag ctc cca gga aga ggc ccc aaa act gtc gtc tct aat     145
Trp Tyr Gln Gln Leu Pro Gly Arg Gly Pro Lys Thr Val Val Ser Asn
        35                  40                  45

aca aat att cgg ccc tcg ggg gtg ccc gat cga ttc tct gcc tcc aag     193
Thr Asn Ile Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Ala Ser Lys
    50                  55                  60

tct ggc agc aca gcc acc ctg acc atc tct ggc ctc cag gct gag gat     241
Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
65                  70                  75                  80

gag gct gat tat tac tgc tca acg tgg gat aat agt ctc agt act tac     289
Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Asn Ser Leu Ser Thr Tyr
                85                  90                  95

atg ttc ggc tct gga acc caa ctg acc gtc ctt ggt cag ccc aag gcc     337
Met Phe Gly Ser Gly Thr Gln Leu Thr Val Leu Gly Gln Pro Lys Ala
            100                 105                 110

tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc     385
Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala
        115                 120                 125

aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc     433
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly
    130                 135                 140

gtg acg gtg gcc tgg aag gca gac ggc agc ccc atc acc cag ggc gtg     481
Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly Val
145                 150                 155                 160

gag acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc     529
Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
                165                 170                 175

agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc     577
Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe
            180                 185                 190

agc tgc ctg gtc acg cac gag ggg agc act gtg gag aag aag gtg gcc     625
Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala
        195                 200                 205

ccc gca gag tgc tct tag gttcccgatg ccccccgccc accgaagggg            673
Pro Ala Glu Cys Ser
    210

gctcggagcc tcaggacctc caggaggatc ttgcctccca tctgggtctt cccagccctt   733

ttccccacac tcaggcaaca ctcaataaag tgtcctttat tcaatcagaa aaaaaaaaaa   793

aaa                                                                 796
```

<210> 35

<211> 213

<212> PRT

<213> Canis familiaris

<400> 35

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

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

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

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

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

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

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

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

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

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

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

Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe
            180                 185                 190

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

Pro Ala Glu Cys Ser
    210
```

<210> 36
<211> 930
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(774)

<223>

<400> 36

atg aag agg gtg aga aat att gaa aag att ata ata aat cag gtg gat 48
Met Lys Arg Val Arg Asn Ile Glu Lys Ile Ile Ile Asn Gln Val Asp
1 5 10 15

```
gtg atg acc tcc acc atg ggc tgg ttc cct ctc atc ctc acc ctc ctc        96
Val Met Thr Ser Thr Met Gly Trp Phe Pro Leu Ile Leu Thr Leu Leu
            20                  25                  30

gct cac tgc gca ggg tcc tgg gcc cag tct gtg ctg act cag ccg gcc       144
Ala His Cys Ala Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Ala
        35                  40                  45

tca gtg tct ggg tcc ctg ggc cag agg gtc acc atc tcc tgc act gga       192
Ser Val Ser Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Thr Gly
    50                  55                  60

agc agc tcc aat gtt ggt tat ggc aat tat gtg ggc tgg tac cag cag       240
Ser Ser Ser Asn Val Gly Tyr Gly Asn Tyr Val Gly Trp Tyr Gln Gln
65                  70                  75                  80

ctc cca gga aca agc ccc aga aac ctc atc tat gat act agt agc cga       288
Leu Pro Gly Thr Ser Pro Arg Asn Leu Ile Tyr Asp Thr Ser Ser Arg
                85                  90                  95

ccc tcg ggg gtc cct gat cga ttc tct ggc tcc agg tca ggc agc aca       336
Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser Gly Ser Thr
            100                 105                 110

gca acc ctg acc atc tct ggg ctc cag gct gag gat gaa gcc gat tat       384
Ala Thr Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
        115                 120                 125

tac tgc tca tcc tat gac aga agt ctc agt ggt gct gtg ttc ggc gga       432
Tyr Cys Ser Ser Tyr Asp Arg Ser Leu Ser Gly Ala Val Phe Gly Gly
    130                 135                 140

ggc acc cac ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc       480
Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val
145                 150                 155                 160

aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc       528
Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr
                165                 170                 175

ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc       576
Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala
            180                 185                 190

tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag       624
Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys
        195                 200                 205

ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc tac ctg agc       672
Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser
    210                 215                 220

ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc       720
Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val
225                 230                 235                 240

acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc       768
Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys
                245                 250                 255

tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc       824
Ser


aggaggatct tgcctcccat ctgggtcatc ccgcccttct ccccgcaccc aggcagcact    884

caataaagtg ttctttgttc aatcagaaaa aaaaaaaaaa aaaaaa                   930
```

<210> 37
<211> 257
<212> PRT
<213> Canis familiaris

<400> 37

```
Met Lys Arg Val Arg Asn Ile Glu Lys Ile Ile Ile Asn Gln Val Asp
1               5                  10                  15

Val Met Thr Ser Thr Met Gly Trp Phe Pro Leu Ile Leu Thr Leu Leu
            20                  25                  30

Ala His Cys Ala Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Ala
        35                  40                  45

Ser Val Ser Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Thr Gly
    50                  55                  60

Ser Ser Ser Asn Val Gly Tyr Gly Asn Tyr Val Gly Trp Tyr Gln Gln
65                  70                  75                  80

Leu Pro Gly Thr Ser Pro Arg Asn Leu Ile Tyr Asp Thr Ser Ser Arg
                85                  90                  95

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser Gly Ser Thr
            100                 105                 110

Ala Thr Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
        115                 120                 125

Tyr Cys Ser Ser Tyr Asp Arg Ser Leu Ser Gly Ala Val Phe Gly Gly
    130                 135                 140

Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val
145                 150                 155                 160

Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr
                165                 170                 175

Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala
            180                 185                 190

Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys
        195                 200                 205

Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser
    210                 215                 220

Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val
225                 230                 235                 240

Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys
                245                 250                 255

                    Ser
```

<210> 38
<211> 843
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (9)..(692)
<223>

<400> 38

```
gcaaacat atg tac aaa att cta gag tct acg tac att gtg aaa aga tca      50
         Met Tyr Lys Ile Leu Glu Ser Thr Tyr Ile Val Lys Arg Ser
         1               5                  10

atc act gtc cct cag cca cca ttt gtg agt gtg acc ctg agg gac acg      98
Ile Thr Val Pro Gln Pro Pro Phe Val Ser Val Thr Leu Arg Asp Thr
15                  20                  25                  30

gcc cac atc acc tgt ggg gga gac aac att gga agt aaa tat gtt caa     146
Ala His Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Tyr Val Gln
                35                  40                  45

tgg atc caa cag aat cca ggt cag gcc ccc gtg gtg att atc tat aga     194
Trp Ile Gln Gln Asn Pro Gly Gln Ala Pro Val Val Ile Ile Tyr Arg
            50                  55                  60

gat acc aag agg ccg aca tgg atc cct gag cga ttc tct ggc gcc aac     242
Asp Thr Lys Arg Pro Thr Trp Ile Pro Glu Arg Phe Ser Gly Ala Asn
        65                  70                  75

tca ggg aac acg gct acc ctg acc atc agt ggg gtc ctg gcc gag gac     290
Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Val Leu Ala Glu Asp
    80                  85                  90

gag gct gac tat tac tgc cag gtg aca gac agt ggt cct cag act aat     338
Glu Ala Asp Tyr Tyr Cys Gln Val Thr Asp Ser Gly Pro Gln Thr Asn
95                  100                 105                 110

gtt ttc ggc gga ggc acc cat ctg acc gtc ctc agt cag ccc aag gcc     386
Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Ser Gln Pro Lys Ala
                115                 120                 125

tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc ggc gcc     434
Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala
            130                 135                 140

aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agt ggc     482
Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly
        145                 150                 155

gtg acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg     530
Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val
    160                 165                 170

gag acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc     578
Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
175                 180                 185                 190

agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc     626
Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe
                195                 200                 205

agc tgc ctg gtc aca cac gag ggg agc acc gtg gag aag aag gtg gcc     674
Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala
            210                 215                 220

ccc gca gag tgc tct tag gttcccgacg cccccgccca cctaaggggg            722
Pro Ala Glu Cys Ser
        225

cccggagcct caggacctcc aggaggatct tgcctcctat ctgggtcatc ccgcccttct   782

ccccacaccc aggcagcact caataaattg ttctttgttc aatcagaaaa aaggggggcc   842

c                                                                   843
```

<210> 39

<211> 227
<212> PRT
<213> Canis familiaris

<400> 39

```
Met Tyr Lys Ile Leu Glu Ser Thr Tyr Ile Val Lys Arg Ser Ile Thr
1               5                  10                  15

Val Pro Gln Pro Pro Phe Val Ser Val Thr Leu Arg Asp Thr Ala His
            20                  25                  30

Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser Lys Tyr Val Gln Trp Ile
        35                  40                  45

Gln Gln Asn Pro Gly Gln Ala Pro Val Val Ile Ile Tyr Arg Asp Thr
    50                  55                  60

Lys Arg Pro Thr Trp Ile Pro Glu Arg Phe Ser Gly Ala Asn Ser Gly
65                  70                  75                  80

Asn Thr Ala Thr Leu Thr Ile Ser Gly Val Leu Ala Glu Asp Glu Ala
                85                  90                  95

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

Gly Gly Gly Thr His Leu Thr Val Leu Ser Gln Pro Lys Ala Ser Pro
        115                 120                 125

Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys
    130                 135                 140

Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr
145                 150                 155                 160

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

Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr
            180                 185                 190

Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys
        195                 200                 205

Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala
    210                 215                 220

Glu Cys Ser
225
```

<210> 40

<211> 858
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (2)..(712)
<223>

<400> 40

```
c tcc aac atg gcc tgg tcc cct ctc ctc ctc aca ctc ctt gct tac tgc      49
  Ser Asn Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Ala Tyr Cys
  1               5                  10                  15

aca ggg tcc tgg gcc cag tct gtg ctg act cag ccg acc tca gtg tcg      97
Thr Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Thr Ser Val Ser
            20                  25                  30

ggg tcc ctt ggc cag agg gtc acc atc tcc tgc tct gga agc acg aac     145
Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Asn
        35                  40                  45

aac atc ggt att gtt ggt gcg agc tgg tac caa cag ctc cca gga aag     193
Asn Ile Gly Ile Val Gly Ala Ser Trp Tyr Gln Gln Leu Pro Gly Lys
    50                  55                  60

gcc cct aaa ctc ctc gtg tac agt gtt ggg gat cga ccg tca ggg gtc     241
Ala Pro Lys Leu Leu Val Tyr Ser Val Gly Asp Arg Pro Ser Gly Val
65                  70                  75                  80

cct gac cgg ttt tcc ggc tcc aac tct ggc aac tca gcc acc ctg acc     289
Pro Asp Arg Phe Ser Gly Ser Asn Ser Gly Asn Ser Ala Thr Leu Thr
                85                  90                  95

atc act ggg ctt cag gct gag gac gag gct gat tat tac tgc cag tcc     337
Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
            100                 105                 110

ttt gat acc acg ctt ggt gct gtg ttc ggc gga ggc acc cac ctg acc     385
Phe Asp Thr Thr Leu Gly Ala Val Phe Gly Gly Gly Thr His Leu Thr
        115                 120                 125

gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg ccc     433
Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro
    130                 135                 140

tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc atc     481
Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile
145                 150                 155                 160

agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca gac ggc     529
Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly
                165                 170                 175

agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag cag agc     577
Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser
            180                 185                 190

aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac aag     625
Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys
```

```
          195                 200                 205

tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag ggg agc      673
Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser
    210                 215                 220

acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag gttcccgacg      722
Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235

gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct tgcctcccat   782

ctgggtcatc ccgcccttct ccccgcaccc aggcagcact caataaagtg ttctttgttc   842

aatcagaaaa aaaaaa                                                   858
```

<210> 41
<211> 236
<212> PRT
<213> Canis familiaris

<400> 41

```
Ser Asn Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Ala Tyr Cys
1               5                  10                  15

Thr Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Thr Ser Val Ser
            20                  25                  30

Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Asn
        35                  40                  45

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

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

Pro Asp Arg Phe Ser Gly Ser Asn Ser Gly Asn Ser Ala Thr Leu Thr
                85                  90                  95

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

Phe Asp Thr Thr Leu Gly Ala Val Phe Gly Gly Gly Thr His Leu Thr
        115                 120                 125

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

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

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

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

Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys
        195                 200                 205

Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser
    210                 215                 220

Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230                 235
```

<210> 42
<211> 514
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (1)..(381)
<223>

<400> 42

```
atg ttc gag gct gtg tca cag tgt gct gtg ttc ggc gga ggc acc cac       48
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                  10                  15

ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc       96
Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc      144
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        35                  40                  45

ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca      192
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
    50                  55                  60

gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag      240
Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
65                  70                  75                  80

cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct      288
Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag      336
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
            100                 105                 110

ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag          381
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct    441

tgcctcccat ctgggtcatc ccgcccttct ccccgcaccc aggcagcact caataaagtg    501

ttctttgttc aat                                                       514
```

<210> 43
<211> 126
<212> PRT
<213> Canis familiaris

<400> 43

```
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                  10                  15

Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

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

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

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

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
            100                 105                 110

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125
```

<210> 44
<211> 514
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(381)
<223>

<400> 44

```
atg ttc gag gct gtg tca cag tgt gct gtg ttc ggc gga ggc acc cac      48
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                   10                  15

ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc      96
Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc     144
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        35                  40                  45

ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca     192
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
    50                  55                  60

gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag     240
Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
65                  70                  75                  80

cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct     288
Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag     336
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu

            100                 105                 110

ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag         381
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct   441

tgcctcccat ctgggtcatc ccgctcttct ccccgcaccc aggcagcact caataaagtg   501

ttctttgttc aat                                                      514
```

<210> 45
<211> 126
<212> PRT
<213> Canis familiaris

<400> 45

```
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                  10                  15

Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

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

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

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

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
            100                 105                 110

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125
```

<210> 46
<211> 561
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(426)
<223>

<400> 46

```
atg ggc ctg ggg cag ggg agg ggc tgc agg ggt gac aga ggg ttt gtg       48
Met Gly Leu Gly Gln Gly Arg Gly Cys Arg Gly Asp Arg Gly Phe Val
1               5                  10                  15

ttc aag gct gta tca ctg tgt tac gtg ttc ggc tca gga acc caa ctg       96
Phe Lys Ala Val Ser Leu Cys Tyr Val Phe Gly Ser Gly Thr Gln Leu
            20                  25                  30
```

```
acc gtc ctt ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg      144
Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro
        35                  40                  45

ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc      192
Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
    50                  55                  60

atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca gac      240
Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp
65                  70                  75                  80

ggc agc ccc atc acc cag ggc gtg gag acc acc aag ccc tcc aag cag      288
Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
                85                  90                  95

agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac      336
Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
            100                 105                 110

aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag ggg      384
Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly
        115                 120                 125

agc act gtg gag aag aag gtg gcc ccc gca gag tgc tct tag              426
Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
    130                 135                 140

gttcccgatg ccccccgccc accgaagggg gctcggagcc tcaggacctc caggaggatc    486

ttgcctccca tctgggtctt cccagccctt ttccccacac tcaggcaaca ctcaataaag    546

tgtcctttat tcaat                                                     561
```

<210> 47
<211> 141
<212> PRT
<213> Canis familiaris

<400> 47

```
Met Gly Leu Gly Gln Gly Arg Gly Cys Arg Gly Asp Arg Gly Phe Val
1               5                  10                  15

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

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

Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
    50                  55                  60

Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp
65                  70                  75                  80

Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
                85                  90                  95

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
            100                 105                 110

Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly
        115                 120                 125

Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
    130                 135                 140
```

<210> 48
<211> 514
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(381)
<223>

<400> 48

```
atg ttc gag gct gtg tca cag tgt gct gtg ttc ggc gga ggc acc cac      48
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                  10                  15

ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc      96
Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc     144
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        35                  40                  45

ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca     192
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
    50                  55                  60

gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag     240
Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
65                  70                  75                  80

cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct     288
Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag     336
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
            100                 105                 110

ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag         381
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125

gttcccgacg gccccgccca cctaaggggg cccggagcct caggacctcc aggaggatct   441

tgcctcccat ctgggtcatc ccgctcttct ccccgcaccc aggcagcact caataaagtg   501

ttctttgttc aat                                                      514
```

<210> 49
<211> 126
<212> PRT
<213> Canis familiaris

<400> 49

```
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                  10                  15
```

Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
20 25 30

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

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

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

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
85 90 95

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
100 105 110

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
115 120 125

<210> 50
<211> 514
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(381)
<223>

<400> 50

```
atg ttc gag gct gtg tca cag tgt gct gtg ttc ggc gga ggc acc cac      48
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                   10                  15

ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc      96
Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc     144
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        35                  40                  45

ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca     192
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala
    50                  55                  60

gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag     240
Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
65                  70                  75                  80

cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct     288
Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag     336
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
            100                 105                 110

ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag         381
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct   441

tgcctcccat ctgggtcatc ccgctcttct ccccgcaccc aggcagcact caataaagtg   501

ttctttgttc aat                                                      514
```

<210> 51
<211> 126
<212> PRT
<213> Canis familiaris

<400> 51

```
Met Phe Glu Ala Val Ser Gln Cys Ala Val Phe Gly Gly Gly Thr His
1               5                   10                  15

Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
            20                  25                  30

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

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

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

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                85                  90                  95

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
            100                 105                 110

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        115                 120                 125
```

<210> 52
<211> 697
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(564)
<223>

<400> 52

```
atg ggc aca cat ggt gac tac caa tca cgg tta gaa ttt caa cca cct      48
Met Gly Thr His Gly Asp Tyr Gln Ser Arg Leu Glu Phe Gln Pro Pro
1               5                   10                  15

gaa tgg tgg gct act ctc aga aat gat cgg gaa aag ctg gag gat ggg      96
Glu Trp Trp Ala Thr Leu Arg Asn Asp Arg Glu Lys Leu Glu Asp Gly
            20                  25                  30

act ctc aga atc cca cgg tgg cac atg aac aaa tac cta gtc acg aca     144
Thr Leu Arg Ile Pro Arg Trp His Met Asn Lys Tyr Leu Val Thr Thr
        35                  40                  45
```

```
gtc ccc gta gag cca gcc agt ctc aaa gag gtg gcc agg aag att ccg      192
Val Pro Val Glu Pro Ala Ser Leu Lys Glu Val Ala Arg Lys Ile Pro
    50                  55                  60

atc cat gat gaa tgt ggt gtg ttc ggc gga ggc acc cac ctg acc gtc      240
Ile His Asp Glu Cys Gly Val Phe Gly Gly Gly Thr His Leu Thr Val
65                  70                  75                  80

ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg ccc tcc      288
Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser
                85                  90                  95

tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc atc agc      336
Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
            100                 105                 110

gac ttc tac ccc agc ggt gtg acg gtg gcc tgg aag gca gac ggc agc      384
Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser
        115                 120                 125

ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag cag agc aac      432
Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn
    130                 135                 140

aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac aag tgg      480
Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp
145                 150                 155                 160

aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag ggg agc acc      528
Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr
                165                 170                 175

gtg gag aag aag gtg gcc ccc gca gag tgc tct tag gttcccgacg           574
Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
            180                 185

gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct tgcctcccat    634

ctgggtcatc ccgcccttct ccccgcaccc aggcagcact caataaagtg ttctttgttc    694

aat                                                                  697
```

<210> 53
<211> 187
<212> PRT
<213> Canis familiaris

<400> 53

```
Met Gly Thr His Gly Asp Tyr Gln Ser Arg Leu Glu Phe Gln Pro Pro
1               5                  10                  15

Glu Trp Trp Ala Thr Leu Arg Asn Asp Arg Glu Lys Leu Glu Asp Gly
            20                  25                  30

Thr Leu Arg Ile Pro Arg Trp His Met Asn Lys Tyr Leu Val Thr Thr
        35                  40                  45

Val Pro Val Glu Pro Ala Ser Leu Lys Glu Val Ala Arg Lys Ile Pro
    50                  55                  60

Ile His Asp Glu Cys Gly Val Phe Gly Gly Gly Thr His Leu Thr Val
65                  70                  75                  80

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

Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
            100                 105                 110

Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser
        115                 120                 125

Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn
    130                 135                 140

Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp
145                 150                 155                 160

Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr
                165                 170                 175

Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
            180                 185
```

<210> 54
<211> 634
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1) .. (501)
<223>

<400> 54

```
atg gaa atg aaa ttc ctg gac ccc agt ggc tat gcc ctc atc acc caa       48
Met Glu Met Lys Phe Leu Asp Pro Ser Gly Tyr Ala Leu Ile Thr Gln
1               5                   10                  15

ccc ccc ttc aac ccg acc agt acc cgt gac aag ggg gct gcc ctt tgg       96
Pro Pro Phe Asn Pro Thr Ser Thr Arg Asp Lys Gly Ala Ala Leu Trp
            20                  25                  30

gcc tcc cga gca gct gca ggg ttt gtg ctc gag gct gtg tca cag tgt      144
Ala Ser Arg Ala Ala Ala Gly Phe Val Leu Glu Ala Val Ser Gln Cys
        35                  40                  45

att gtg ttc ggc gga ggc acc cat ctg acc gtc ctc ggt cag ccc aag      192
Ile Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys
    50                  55                  60

gcc tcc cct tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctt ggc      240
Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly
65                  70                  75                  80

gcc aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc      288
Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser
                85                  90                  95

ggc gtg aca gtg gcc tgg aag gca gac ggc agc ccc atc acc cag ggt      336
Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly
            100                 105                 110

gtg gag acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc      384
Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
        115                 120                 125


agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc      432
Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser
    130                 135                 140

ttc agc tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg      480
Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val
145                 150                 155                 160

gcc ccc gca gag tgc tct tag gttcctgatg tcccccgccc accaaagggg         531
Ala Pro Ala Glu Cys Ser
                165

gctcagagcc tcaggacctc caggaggatc ttgcctccca tctgggtcat cccagccttt    591

ccccttaaac ccaggcaaca ttcaataaag tgttctttct tca                     634
```

<210> 55

<211> 166

<212> PRT

<213> Canis familiaris

<400> 55

```
Met Glu Met Lys Phe Leu Asp Pro Ser Gly Tyr Ala Leu Ile Thr Gln
1               5                  10                  15

Pro Pro Phe Asn Pro Thr Ser Thr Arg Asp Lys Gly Ala Ala Leu Trp
            20                  25                  30

Ala Ser Arg Ala Ala Ala Gly Phe Val Leu Glu Ala Val Ser Gln Cys
        35                  40                  45

Ile Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys
    50                  55                  60

Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly
65                  70                  75                  80

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

Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly
            100                 105                 110

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

Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser
    130                 135                 140

Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val
145                 150                 155                 160

Ala Pro Ala Glu Cys Ser
                165
```

<210> 56
<211> 551
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (39)..(419)
<223>

<400> 56

```
ggtcatggat atgacacagc tgtaccccca caccaaga atg agg cag ttg ctg aca      56
                                          Met Arg Gln Leu Leu Thr
                                          1               5

caa caa aca tct gcc ttg acc cgc tgt cct tcc atc ccc aca ggt cag      104
Gln Gln Thr Ser Ala Leu Thr Arg Cys Pro Ser Ile Pro Thr Gly Gln
            10                  15                  20

ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag      152
Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        25                  30                  35

ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac      200
Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    40                  45                  50

ccc agt ggc gtg acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc      248
Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr
55                  60                  65                  70

cag ggc gtg gag acc acc aag ccc tcc aag cag agc aac aac aag tac      296
Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                75                  80                  85

gcg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac      344
Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
            90                  95                  100

agc agc ttc agc tgc ctg gtc aca cac gag ggg agc acc gtg gag aag      392
Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys
        105                 110                 115

aag gtg gcc ccc gca gag tgc tct tag gttcccgacg cccccgccca            439
Lys Val Ala Pro Ala Glu Cys Ser
    120                 125

cctaaggggg cccggagcct caggacctcc aggaggatct tgcctcctat ctgggtcatc    499

ccgcccttct ccccacaccc aggcagcact caataaagtg ttctttgttc aa            551
```

<210> 57
<211> 126
<212> PRT
<213> Canis familiaris

<400> 57

```
Met Arg Gln Leu Leu Thr Gln Gln Thr Ser Ala Leu Thr Arg Cys Pro
1               5                   10                  15

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

Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        35                  40                  45
```

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

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

Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro
85 90 95

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu
100 105 110

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
115 120 125

<210> 58
<211> 864
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(702)
<223>

<400> 58

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt      48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc      96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg     144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg     192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc     240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc     288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa agt agc     336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
            100                 105                 110

gct gat tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt     384
Ala Asp Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly
        115                 120                 125

cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag     432
Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu
    130                 135                 140

gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc     480
Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145                 150                 155                 160

tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc     528
Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile
                165                 170                 175

atc cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag     576
Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys
            180                 185                 190

tac acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct     624
Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
        195                 200                 205

cac agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag     672
His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
    210                 215                 220

aag aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga      722
Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    782

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    842

aagactttat catttatcac tg                                           864
```

<210> 59
<211> 233
<212> PRT
<213> Canis familiaris

<400> 59

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
            100                 105                 110

Ala Asp Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly
        115                 120                 125

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

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

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

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

Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
        195                 200                 205

His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
    210                 215                 220

Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 60

<211> 864
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(702)
<223>

<400> 60

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa agt agc      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
            100                 105                 110

gct gat gct cac aac aac tct gga aga aaa att gga gca cct ggc agt      384
Ala Asp Ala His Asn Asn Ser Gly Arg Lys Ile Gly Ala Pro Gly Ser
        115                 120                 125

cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag      432
Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu
```

```
    130                 135                 140

gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc      480
Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
145                 150                 155                 160

tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc      528
Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile
                165                 170                 175

atc cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag      576
Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys
            180                 185                 190

tac acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct      624
Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
        195                 200                 205

cac agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag      672
His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
    210                 215                 220

aag aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga      722
Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    782

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    842

aagactttat catttatcac tg                                           864
```

<210> 61

<211> 233

<212> PRT

<213> Canis familiaris

<400> 61

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
            100                 105                 110

Ala Asp Ala His Asn Asn Ser Gly Arg Lys Ile Gly Ala Pro Gly Ser
        115                 120                 125

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

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

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

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

Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
        195                 200                 205

His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
    210                 215                 220

Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 62
<211> 867
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (1)..(705)
<223>

<400> 62

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa agt agc      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
            100                 105                 110

agt aaa aat tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc      384
```

```
Ser Lys Asn Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu
        115                 120                 125

ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct      432
Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser
    130                 135                 140

gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac      480
Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145                 150                 155                 160

ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc      528
Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr
                165                 170                 175

atc atc cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac      576
Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
            180                 185                 190

aag tac acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa      624
Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
        195                 200                 205

tct cac agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg      672
Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val
    210                 215                 220

gag aag aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga    725
Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    785

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    845

aagactttat catttatcac tg                                            867
```

<210> 63
<211> 234
<212> PRT
<213> Canis familiaris

<400> 63

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser

            100                 105                 110

Ser Lys Asn Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu
        115                 120                 125

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

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

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

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

Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
        195                 200                 205

Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val
    210                 215                 220

Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 64
<211> 861
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(699)
<223>

<400> 64

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95
```

```
caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa aat aaa      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Asn Lys
                100                 105                 110

tat tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag      384
Tyr Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag      432
Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac      480
Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc      528
Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile
                165                 170                 175

cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac      576
Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac      624
Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag      672
Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga           719
Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    779

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    839

aagactttat catttatcac tg                                           861
```

<210> 65
<211> 232
<212> PRT
<213> Canis familiaris

<400> 65

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Asn Lys
            100                 105                 110

Tyr Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

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

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

Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 66
<211> 861
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (1)..(699)
<223>

<400> 66

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80
```

```
tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa atc tct      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ile Ser
            100                 105                 110

gtg tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag      384
Val Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag      432
Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac      480
Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc      528
Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile
                165                 170                 175

cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac      576
Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac      624
Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag      672
Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga            719
Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    779

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    839

aagactttat catttatcac tg                                            861
```

<210> 67
<211> 232
<212> PRT
<213> Canis familiaris

<400> 67

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ile Ser
            100                 105                 110

Val Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

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

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

Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 68
<211> 867
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (1)..(705)
<223>

<400> 68

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                   10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
```

```
     50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gag atg cac aca cct      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Glu Met His Thr Pro
            100                 105                 110

gaa tca cag tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc      384
Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu
        115                 120                 125

ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct      432
Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser
    130                 135                 140

gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac      480
Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145                 150                 155                 160

ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc      528
Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr
                165                 170                 175

atc atc cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac      576
Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
            180                 185                 190

aag tac acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa      624
Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
        195                 200                 205

tct cac agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg      672
Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val
    210                 215                 220

gag aag aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga    725
Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    785

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    845

aagactttat catttatcac tg                                            867
```

<210> 69
<211> 234
<212> PRT
<213> Canis familiaris

<400> 69

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Glu Met His Thr Pro
            100                 105                 110

Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu
        115                 120                 125

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

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

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

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

Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
        195                 200                 205

Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val
    210                 215                 220

Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 70
<211> 861
<212> DNA
<213> Canis familiaris

<220>
<221> CDS

<222> (1)..(699)
<223>

<400> 70

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                   10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
```

```
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag cat tac cac cat gac      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln His Tyr His His Asp
            100                 105                 110

tat tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag      384
Tyr Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag      432
Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac      480
Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc      528
Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile
                165                 170                 175

cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac      576
Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac      624
Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag      672
Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga            719
Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    779

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    839

aagactttat catttatcac tg                                            861
```

<210> 71
<211> 232
<212> PRT
<213> Canis familiaris

<400> 71

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr

            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln His Tyr His His Asp
            100                 105                 110

Tyr Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

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

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

Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 72
<211> 861
<212> DNA
<213> Canis familiaris

<220>

<221> CDS
<222> (1)..(699)
<223>

<400> 72

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                   10                  15
```

```
tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc      96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg     144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg     192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc     240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc     288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gtc cat ggg ggg gga     336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val His Gly Gly Gly
            100                 105                 110

ggg tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag     384
Gly Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag     432
Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac     480
Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc     528
Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile
                165                 170                 175

cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac     576
Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac     624
Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag     672
Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga           719
Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    779

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata   839

aagactttat catttatcac tg                                           861
```

<210> 73
<211> 232
<212> PRT
<213> Canis familiaris

<400> 73

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val His Gly Gly Gly
            100                 105                 110

Gly Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

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

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

Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 74
<211> 861
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(699)
<223>

<400> 74

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt      48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc      96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg     144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg     192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc     240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc     288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag aaa cat cgg ggt gca     336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Lys His Arg Gly Ala
            100                 105                 110

ggt tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag     384
Gly Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag     432
Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac     480
Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc     528
Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile
                165                 170                 175

cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac     576
Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac     624
Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag     672
Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga           719
Lys Val Ala Pro Ala Glu Cys Ser
225                 230

tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac    779

cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata    839

aagactttat catttatcac tg                                           861
```

<210> 75

<211> 232
<212> PRT
<213> Canis familiaris

<400> 75

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Lys His Arg Gly Ala
            100                 105                 110

Gly Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

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

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

Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His
        195                 200                 205

Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys
    210                 215                 220

Lys Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 76

<211> 858
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(696)
<223>

<400> 76

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt       48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc       96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg      144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg      192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc      240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc      288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gtg tcc ctt ggg tct      336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Ser Leu Gly Ser
            100                 105                 110

tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag ccc      384
Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc      432
Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac ccc      480
Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc cag      528
Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile Gln
                165                 170                 175

ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac acg      576
Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Thr
            180                 185                 190

gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc      624
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser
        195                 200                 205

agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag aag      672
Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys Lys
    210                 215                 220

gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga tggagccttc      726
Val Ala Pro Ala Glu Cys Ser
225                 230

ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac cctggaccag      786

ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata aagactttat      846


catttatcac tg                                                         858
```

<210> 77
<211> 231
<212> PRT
<213> Canis familiaris

<400> 77

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Ser Leu Gly Ser
            100                 105                 110

Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile Gln
                165                 170                 175

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

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser
        195                 200                 205

Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys Lys
    210                 215                 220

Val Ala Pro Ala Glu Cys Ser
225                 230
```

<210> 78
<211> 858
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(696)
<223>

<400> 78

```
atg gcc tgg acc ctt ctt ctc ctt gga ttc ctg gct cac tgc aca ggt      48
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc      96
Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg     144
Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg     192
Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc     240
Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc     288
Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

caa acc aac gat gag gct gac tat tac tgc cag gta ttg atg gga ggg     336
Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Leu Met Gly Gly
            100                 105                 110

tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag ccc     384
Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc     432
Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac ccc     480
Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc cag     528
Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile Gln
                165                 170                 175

ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac acg     576
Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Thr
            180                 185                 190

gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc     624
Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser
        195                 200                 205

agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag aag     672
Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys Lys
    210                 215                 220

gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga tggagccttc     726
Val Ala Pro Ala Glu Cys Ser
225                 230

ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaacccac cctggaccag     786

ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata aagactttat     846

catttatcac tg                                                        858
```

<210> 79

<211> 231
<212> PRT
<213> Canis familiaris

<400> 79

```
Met Ala Trp Thr Leu Leu Leu Leu Gly Phe Leu Ala His Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr
            20                  25                  30

Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg
        35                  40                  45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
    50                  55                  60

Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
                85                  90                  95

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Leu Met Gly Gly
            100                 105                 110

Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile Gln
                165                 170                 175

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

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser
        195                 200                 205

Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys Lys
    210                 215                 220

                    Val Ala Pro Ala Glu Cys Ser
                    225                 230
```

<210> 80

<211> 834
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(672)
<223>

<400> 80

```
atg tcc tct ctt gca ggt tcc atg gct gcc aac aag ctg act caa tcc       48
Met Ser Ser Leu Ala Gly Ser Met Ala Ala Asn Lys Leu Thr Gln Ser
1               5                   10                  15

ctg ttt atg tca gtg gcc ctg gga cag atg gcc agg atc acc tgt ggg       96
Leu Phe Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly
            20                  25                  30

aga gac aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca      144
Arg Asp Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro
        35                  40                  45

agc cag gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca      192
Ser Gln Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser
    50                  55                  60

gga ttc tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc      240
Gly Phe Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr
65                  70                  75                  80

ctg acc att agt ggg ccc cca gcg agg acg cag gtc agg tat gcc cag      288
Leu Thr Ile Ser Gly Pro Pro Ala Arg Thr Gln Val Arg Tyr Ala Gln
                85                  90                  95

ccc ggg gct cca ggg gca ggg act tgt tgg gta ttc ggt gaa ggg acc      336
Pro Gly Ala Pro Gly Ala Gly Thr Cys Trp Val Phe Gly Glu Gly Thr
            100                 105                 110

cag ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc      384
Gln Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu
        115                 120                 125

ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg      432
Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val
    130                 135                 140

tgc ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag      480
Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys
145                 150                 155                 160

gca gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc      528
Ala Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser
                165                 170                 175

aag cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg      576
Lys Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr
            180                 185                 190

cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac      624
Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His
        195                 200                 205

cag ggg agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag      672
Gln Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
```

210 215 220

gtccctgaga attcctgaga tggagccttc ctcacccaga caccccttcc ccagttcacc 732

ttgtgcccct gaaaacccac cctggaccag ctcagaccag gcaggtcact catcctccct 792

gtttctactt gtgctcaata aagactttat catttatcac tg 834

<210> 81
<211> 223
<212> PRT
<213> Canis familiaris

<400> 81

```
Met Ser Ser Leu Ala Gly Ser Met Ala Ala Asn Lys Leu Thr Gln Ser
1               5                   10                  15

Leu Phe Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly
            20                  25                  30

Arg Asp Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro
        35                  40                  45

Ser Gln Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser
    50                  55                  60

Gly Phe Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr
65                  70                  75                  80

Leu Thr Ile Ser Gly Pro Pro Ala Arg Thr Gln Val Arg Tyr Ala Gln
                85                  90                  95

Pro Gly Ala Pro Gly Ala Gly Thr Cys Trp Val Phe Gly Glu Gly Thr
            100                 105                 110

Gln Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu
        115                 120                 125

Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val
    130                 135                 140

Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys
145                 150                 155                 160

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

Lys Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr
            180                 185                 190

Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His
        195                 200                 205

Gln Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
    210                 215                 220
```

<210> 82
<211> 780
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(618)
<223>

<400> 82

```
atg tca gtg gcc ctg gga cag atg gcc agg atc acc tgt ggg aga gac        48
Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly Arg Asp
1               5                   10                  15

aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag        96
Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc       144
Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc       192
Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

att aaa gaa atg gac gca ttc ctg gaa acc tcc ttc tat tgc tgg atg       240
Ile Lys Glu Met Asp Ala Phe Leu Glu Thr Ser Phe Tyr Cys Trp Met
65                  70                  75                  80

tgg cag cct gaa tca cag tgt tgg gta ttc ggt gaa ggg acc cag ctg       288
Trp Gln Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr Gln Leu
                85                  90                  95

acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg       336
Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro
            100                 105                 110

ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc       384
Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
        115                 120                 125

atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat       432
Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp
    130                 135                 140

ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag cag       480
Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
145                 150                 155                 160

agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct gac       528
Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
                165                 170                 175

aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag ggg       576
Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly
            180                 185                 190

agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag               618
Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205

gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc     678

ttgtgccccc gaaaacccac cctggaccag ctcagaccag gcaggtcact catcctccct     738

gtttctactt gtgctcaata aagactttat catttatcac tg                       780
```

<210> 83
<211> 205
<212> PRT
<213> Canis familiaris

<400> 83

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

Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

Ile Lys Glu Met Asp Ala Phe Leu Glu Thr Ser Phe Tyr Cys Trp Met
65                  70                  75                  80

Trp Gln Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr Gln Leu
                85                  90                  95

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

Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
        115                 120                 125

Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp
    130                 135                 140

Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
145                 150                 155                 160

Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
                165                 170                 175

Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly
            180                 185                 190

Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205
```

<210> 84
<211> 786
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(624)
<223>

<400> 84

```
atg tca gtg gcc ctg gga cag atg gcc agg atc acc tgt ggg aga gac      48
Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly Arg Asp
1               5                   10                  15

aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag      96
Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc     144
Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc     192
Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

att agt gtg tca aac att gac gac acg ctt tac ata tat aga acg gaa     240
Ile Ser Val Ser Asn Ile Asp Asp Thr Leu Tyr Ile Tyr Arg Thr Glu
65                  70                  75                  80

gtg agc aac att cct gaa tca cag tgt tgg gta ttc ggt gaa ggg acc     288
Val Ser Asn Ile Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr
                85                  90                  95

cag ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc     336
Gln Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu
            100                 105                 110

ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg     384
Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val
        115                 120                 125

tgc ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag     432
Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys
    130                 135                 140

gca gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc     480
Ala Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser
145                 150                 155                 160

aag cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg     528
Lys Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr
                165                 170                 175

cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac     576
Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His
            180                 185                 190

cag ggg agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag     624
Gln Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205

gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc    684

ttgtgcccct gaaaacccac cctggaccag ctcagaccag gcaggtcact catcctccct    744

gtttctactt gtgctcaata aagactttat catttatcac tg                      786
```

<210> 85
<211> 207
<212> PRT
<213> Canis familiaris

<400> 85

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

Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

Ile Ser Val Ser Asn Ile Asp Asp Thr Leu Tyr Ile Tyr Arg Thr Glu
65                  70                  75                  80

Val Ser Asn Ile Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr
                85                  90                  95

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

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

Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys
    130                 135                 140

Ala Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser
145                 150                 155                 160

Lys Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr
                165                 170                 175

Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His
            180                 185                 190

Gln Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205
```

<210> 86
<211> 783
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1) .. (621)
<223>

<400> 86

```
atg tca gtg gcc ctg gga cag atg gcc agg atc acc tgt ggg aga gac        48
Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly Arg Asp
1               5                   10                  15

aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag        96
Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc       144

Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc       192
Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

att agt gga cac cgt gca gaa cca gag gca gaa cat ttc tct ctg tgg       240
Ile Ser Gly His Arg Ala Glu Pro Glu Ala Glu His Phe Ser Leu Trp
65                  70                  75                  80

cca tgc aag tca gat cct ggt tgt tgg gta ttc ggt gaa ggg acc cag       288
Pro Cys Lys Ser Asp Pro Gly Cys Trp Val Phe Gly Glu Gly Thr Gln
                85                  90                  95

ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc       336
Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe
            100                 105                 110

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc       384
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        115                 120                 125

ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca       432
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala
    130                 135                 140

gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag       480
Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
145                 150                 155                 160

cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct       528
Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                165                 170                 175

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag       576
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln
            180                 185                 190

ggg agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag           621
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205

gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc     681

ttgtgcccct gaaaacccac cctggaccag ctcagaccag gcaggtcact catcctccct     741

gtttctactt gtgctcaata aagactttat catttatcac tg                       783
```

<210> 87
<211> 206
<212> PRT
<213> Canis familiaris

<400> 87

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

Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr

    50                  55                  60

Ile Ser Gly His Arg Ala Glu Pro Glu Ala Glu His Phe Ser Leu Trp
65                  70                  75                  80

Pro Cys Lys Ser Asp Pro Gly Cys Trp Val Phe Gly Glu Gly Thr Gln
                85                  90                  95

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

Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
        115                 120                 125

Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala
    130                 135                 140

Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
145                 150                 155                 160

Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro
                165                 170                 175

Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln
            180                 185                 190

Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205
```

<210> 88
<211> 780
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(618)
<223>

<400> 88

```
atg tca gtg gcc ctg gga cag atg gcc agg atc acc tgt ggg aga gac      48
Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly Arg Asp
1               5                   10                  15

aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag      96
Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc     144
Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc     192
Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

att agt cag atc cca ccc tac tct gaa gtg act cgc ttc act cgg gcc     240
Ile Ser Gln Ile Pro Pro Tyr Ser Glu Val Thr Arg Phe Thr Arg Ala
65                  70                  75                  80

tgg gca gac act agc tgt tgt tgg gta ttc ggt gaa ggg acc cag ctg     288
Trp Ala Asp Thr Ser Cys Cys Trp Val Phe Gly Glu Gly Thr Gln Leu
                85                  90                  95

acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg     336
Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro
            100                 105                 110

ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc     384
Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
        115                 120                 125

atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat     432
Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp
    130                 135                 140

ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag cag     480
Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
145                 150                 155                 160

agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct gac     528
Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
                165                 170                 175

aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag ggg     576
Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly
            180                 185                 190

agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag             618
Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205

gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc    678

ttgtgcccct gaaaacccac cctggaccag ctcagaccag gcaggtcact catcctccct    738

gtttctactt gtgctcaata aagactttat catttatcac tg                      780
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<210> 89
<211> 205
<212> PRT
<213> Canis familiaris

<400> 89

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

Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln
            20                  25                  30

Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe
        35                  40                  45

Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr
    50                  55                  60

Ile Ser Gln Ile Pro Pro Tyr Ser Glu Val Thr Arg Phe Thr Arg Ala
65                  70                  75                  80

Trp Ala Asp Thr Ser Cys Cys Trp Val Phe Gly Glu Gly Thr Gln Leu
                85                  90                  95

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

Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
        115                 120                 125

Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp
    130                 135                 140

Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
145                 150                 155                 160

Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
                165                 170                 175

Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly
            180                 185                 190

Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
        195                 200                 205
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<210> 90
<211> 851
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (24)..(719)
<223>

<400> 90

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                         Met Ala Trp Thr His Leu Leu Leu Ser Leu
                         1               5                  10

ctg gct ctc tgc aca ggt tct gtg gcc tcc tat gtg ctg aca cag ctg      101
Leu Ala Leu Cys Thr Gly Ser Val Ala Ser Tyr Val Leu Thr Gln Leu
                15                  20                  25

cca tcc aaa aat gtg acc ctg aag cag ccg gcc cac atc acc tgt ggg      149
Pro Ser Lys Asn Val Thr Leu Lys Gln Pro Ala His Ile Thr Cys Gly
            30                  35                  40

gga gac aac att gga agt aaa agt gtt cac tgg tac cag cag aag ctg      197
Gly Asp Asn Ile Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Leu
        45                  50                  55

ggc cag gcc cct gta ctg att atc tat tat gat agc agc agg ccg aca      245
Gly Gln Ala Pro Val Leu Ile Ile Tyr Tyr Asp Ser Ser Arg Pro Thr
    60                  65                  70

ggg atc cct gag cga ttc tcc ggc gcc aac tcg ggg aac acg gcc acc      293
Gly Ile Pro Glu Arg Phe Ser Gly Ala Asn Ser Gly Asn Thr Ala Thr
75                  80                  85                  90

ctg acc atc agc ggg gcc ctg gcc gag gac gag gct gac tat tac tgc      341
Leu Thr Ile Ser Gly Ala Leu Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
                95                  100                 105

cag gtg tgg gac agc agt gct ctt gtg ttc ggc gga ggc acc cat ctg      389
Gln Val Trp Asp Ser Ser Ala Leu Val Phe Gly Gly Gly Thr His Leu
            110                 115                 120


acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg      437
Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro
        125                 130                 135

ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc      485
Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu
    140                 145                 150

atc agc gac ttc tac ccc agt ggc gtg acg gtg gcc tgg aag gca gac      533
Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp
155                 160                 165                 170

ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag cag      581
Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln
                175                 180                 185

agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac      629
Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp
            190                 195                 200

aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc aca cac gag ggg      677
Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly
        205                 210                 215

agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag               719
Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
    220                 225                 230

gttcccgacg cccccgccca cctaaggggg cccggagcct caggacctcc aggaggatct    779

tgcctcctat ctgggtcatc ccgcccttct ccccacaccc aggcagcact caataaagtg    839

ttctttgttc aa                                                        851
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<210> 91
<211> 231
<212> PRT
<213> Canis familiaris

<400> 91

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Met Ala Trp Thr His Leu Leu Leu Ser Leu Leu Ala Leu Cys Thr Gly
1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Leu Pro Ser Lys Asn Val Thr
            20                  25                  30

Leu Lys Gln Pro Ala His Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser
        35                  40                  45

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

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

Ser Gly Ala Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Ala
                85                  90                  95

Leu Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser
            100                 105                 110

Ala Leu Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro
        115                 120                 125

Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
    130                 135                 140

Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
145                 150                 155                 160

Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln
                165                 170                 175

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

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser
        195                 200                 205

Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys
    210                 215                 220

Val Ala Pro Ala Glu Cys Ser
225                 230
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<210> 92
<211> 881
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (18)..(719)
<223>

<400> 92

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                   Met Ala Trp Thr His Leu Leu Leu Ser Leu Leu
                   1               5                   10

gct ctc tgc aca ggt tct gtg gcc tcc tat gtg ctg aca cag ctg cca        98
Ala Leu Cys Thr Gly Ser Val Ala Ser Tyr Val Leu Thr Gln Leu Pro
               15                  20                  25

tcc aaa aat gtg acc ctg aag cag ccg gcc cac atc acc tgt ggg gga       146
Ser Lys Asn Val Thr Leu Lys Gln Pro Ala His Ile Thr Cys Gly Gly
           30                  35                  40

gac aac att gga agt aaa agt gtt cac tgg tac cag cag aag ctg ggc       194
Asp Asn Ile Gly Ser Lys Ser Val His Trp Tyr Gln Gln Lys Leu Gly
       45                  50                  55

cag gcc cct gta ctg att atc tat tat gat agc agc agg ccg aca ggg       242
Gln Ala Pro Val Leu Ile Ile Tyr Tyr Asp Ser Ser Arg Pro Thr Gly
60                 65                  70                  75

atc cct gag cga ttc tcc ggc gcc aac tcg ggg aac acg gcc acc ctg       290
Ile Pro Glu Arg Phe Ser Gly Ala Asn Ser Gly Asn Thr Ala Thr Leu
                   80                  85                  90

acc atc agc ggg gcc ctg gcc gag gac gag gct gac tat tac tgc cag       338
Thr Ile Ser Gly Ala Leu Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
```

```
                95                  100                 105

gtg tgg gac agc agt ggt cat tgt tgg gta ttc ggt gaa ggg acc cag      386
Val Trp Asp Ser Ser Gly His Cys Trp Val Phe Gly Glu Gly Thr Gln
        110                 115                 120

ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc      434
Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe
    125                 130                 135

ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc      482
Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
140                 145                 150                 155

ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca      530
Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala
                160                 165                 170

gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag      578
Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys
            175                 180                 185

cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct      626
Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro
        190                 195                 200

gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag      674
Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln
    205                 210                 215

ggg agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag          719
Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
220                 225                 230

gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc    779

ttgtgccccc gaaaacccac cctggaccag ctcagaccag gcaggtcact catcctccct    839

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<210> 93
<211> 233
<212> PRT
<213> Canis familiaris

<400> 93

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1               5                  10                  15

Ser Val Ala Ser Tyr Val Leu Thr Gln Leu Pro Ser Lys Asn Val Thr
            20                  25                  30

Leu Lys Gln Pro Ala His Ile Thr Cys Gly Gly Asp Asn Ile Gly Ser
        35                  40                  45

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

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

Ser Gly Ala Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Ala
                85                  90                  95

Leu Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser
            100                 105                 110

Gly His Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly
        115                 120                 125

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

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

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

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

Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
        195                 200                 205

His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
    210                 215                 220

Lys Lys Val Ala Pro Ala Glu Cys Ser
225                 230
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<210> 94
<211> 935
<212> DNA
<213> Bos taurus

<220>
<221> CDS
<222> (55)..(762)

<223>

<400> 94

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ggctctgctc agctgtgggg ccacagacgg caggacgccc tgaccatgtc cacc atg        57
                                                              Met
                                                               1

gcc tgg tcc cct ctg ctc ctc acc ctg gtc gct ctc tgc aca gga tcc        105
Ala Trp Ser Pro Leu Leu Leu Thr Leu Val Ala Leu Cys Thr Gly Ser
            5                  10                  15

tgg gcc cag gct gtg ctg act cag ccg tcc tcc gtg tcc ggc tcc ctg        153
Trp Ala Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ser Leu
        20                  25                  30

ggc cag agg gtc tcc atc acc tgc tct gga agc agc acg aat atc ggc        201
Gly Gln Arg Val Ser Ile Thr Cys Ser Gly Ser Ser Thr Asn Ile Gly
    35                  40                  45

att tat ggt gta aac tgg tac caa cag gtc cca gga tcg ggc ctc aaa        249
Ile Tyr Gly Val Asn Trp Tyr Gln Gln Val Pro Gly Ser Gly Leu Lys
50                  55                  60                  65

acc atc atc tat gaa gat aag tat cga ccc tcg ggg gtc ccc gac cga        297
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Thr Ile Ile Tyr Glu Asp Lys Tyr Arg Pro Ser Gly Val Pro Asp Arg
                70                  75                  80

ttc tcc ggc tcc aag tct ggc aac aca gcc acc cta acc atc aac tcg      345
Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Thr Leu Thr Ile Asn Ser
            85                  90                  95

ctc cag gct gag gac gag gcg gat tat ttc tgt gca gct ggt gac tac      393
Leu Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ala Ala Gly Asp Tyr
        100                 105                 110

agt gtc aat act gcc gtt ttc ggc ggc ggg acc aca ctg acc gtc ctg      441
Ser Val Asn Thr Ala Val Phe Gly Gly Gly Thr Thr Leu Thr Val Leu
    115                 120                 125

ggt cag ccc aag tcc cca ccc tcg gtc acc ctg ttc ccg ccc tcc acg      489
Gly Gln Pro Lys Ser Pro Pro Ser Val Thr Leu Phe Pro Pro Ser Thr
130                 135                 140                 145

gag gag ctc aac ggc aac aag gcc acc ctg gtg tgt ctc atc agc gac      537
Glu Glu Leu Asn Gly Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
                150                 155                 160

ttc tac ccg ggt agc gtg acc gtg gtc tgg aag gca gac ggc agc acc      585
Phe Tyr Pro Gly Ser Val Thr Val Val Trp Lys Ala Asp Gly Ser Thr
            165                 170                 175

atc acc cgc aac gtg gag acc acc cgg gcc tcc aaa cag agc aac agc      633
Ile Thr Arg Asn Val Glu Thr Thr Arg Ala Ser Lys Gln Ser Asn Ser
        180                 185                 190

aag tac gcg gcc agc agc tac ctg agc ctg acg agc agc gac tgg aaa      681
Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Ser Ser Asp Trp Lys
    195                 200                 205

tcg aaa ggc agt tac agc tgc gag gtc acg cac gag ggg agc acc gtg      729
Ser Lys Gly Ser Tyr Ser Cys Glu Val Thr His Glu Gly Ser Thr Val
210                 215                 220                 225

acg aag aca gtg aag ccc tca gag tgt tct tag ggccctggac ccccaccctc    782
Thr Lys Thr Val Lys Pro Ser Glu Cys Ser
                230                 235

gggggccctc tggcccacac cccctccccc acctctccat ggacccctga gcccctaccc    842

aggtcgcctc acaccagggg cctctcctcc ctccctgttc ctgcttctcc tgaataaaga    902

ccttctcatt tatcaacaaa aaaaaaaaaa aaa                                 935
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<210> 95
<211> 235
<212> PRT
<213> Bos taurus

<400> 95

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1               5                  10                  15

Ser Trp Ala Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ser
            20                  25                  30

Leu Gly Gln Arg Val Ser Ile Thr Cys Ser Gly Ser Ser Thr Asn Ile
        35                  40                  45

Gly Ile Tyr Gly Val Asn Trp Tyr Gln Gln Val Pro Gly Ser Gly Leu

    50                  55                  60

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

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

Ser Leu Gln Ala Glu Asp Glu Ala Asp Tyr Phe Cys Ala Ala Gly Asp
            100                 105                 110

Tyr Ser Val Asn Thr Ala Val Phe Gly Gly Gly Thr Thr Leu Thr Val
        115                 120                 125

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

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

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

Thr Ile Thr Arg Asn Val Glu Thr Thr Arg Ala Ser Lys Gln Ser Asn
            180                 185                 190

Ser Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Ser Ser Asp Trp
        195                 200                 205

Lys Ser Lys Gly Ser Tyr Ser Cys Glu Val Thr His Glu Gly Ser Thr
    210                 215                 220

Val Thr Lys Thr Val Lys Pro Ser Glu Cys Ser
225                 230                 235
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<210> 96
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<212> DNA
<213> Artificial

<220>
<223> T3 primer

<400> 96
aattaaccct cactaaaggg 20

<210> 97
<211> 19
<212> DNA
<213> Artificial

<220>
<223> T7 primer

<400> 97
taatacgact cactatagg 19

<210> 98
<211> 18
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 98
ctgaccgtcc tcggtcag 18

<210> 99
<211> 18
<212> DNA
<213> Artificial

<220>
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<400> 99
ccttcttctc cacggtgc 18

<210> 100
<211> 18
<212> DNA
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<220>
<223> primer

<400> 100
tggtaaccca tggcctgc 18

<210> 101
<211> 18
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 101
accgtcttct ccacggtg 18

<210> 102
<211> 18
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<213> Artificial

<220>
<223> GAPDH primer

<400> 102
gggctgcttt taactctg 18

<210> 103
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<212> DNA
<213> Artificial

<220>
<223> GAPDH primer

<400> 103
ccaggaaatg agcttgac 18

<210> 104
<211> 24
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 104
catatgttcg gcggaggcac ccac 24

<210> 105
<211> 24
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 105
ggtaccagag cactctgcgg gggc 24

<210> 106
<211> 23
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 106
gaattcctgc tgcgcccaac agc 23

<210> 107
<211> 24
<212> DNA
<213> Artificial

<220>
<223> primer

<400> 107
gtcgacctat gaacattctg cagg 24

<210> 108
<211> 10
<212> PRT
<213> Homo sapiens

<400> 108

Leu Leu Arg Pro Thr Ala Ala Ser Gln Ser
1 5 10

<210> 109
<211> 9
<212> PRT
<213> Homo sapiens

<400> 109

Ala Leu Gly Pro Gly Ala Pro Gly Gly

1 5

<210> 110
<211> 10
<212> PRT
<213> Homo sapiens

<400> 110

Ser Leu Arg Ser Arg Trp Gly Arg Phe Leu
1 5 10

<210> 111
<211> 10
<212> PRT
<213> Homo sapiens

<400> 111

Ser Lys His Asn Ser Val Thr His Val Phe
1 5 10

<210> 112

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

<400> 112

Lys His Asn Ser Val Thr His Val Phe
1 5

<210> 113
<211> 10
<212> PRT
<213> Homo sapiens

<400> 113

Ser Val Thr His Val Phe Gly Ser Gly Thr
1 5 10

<210> 114
<211> 9
<212> PRT
<213> Homo sapiens

<400> 114

Val Thr His Val Phe Gly Ser Gly Thr
1 5

<210> 115
<211> 9
<212> PRT
<213> Homo sapiens

<400> 115

Val Phe Gly Ser Gly Thr Gln Leu Thr
1 5

<210> 116
<211> 9
<212> PRT
<213> Homo sapiens

<400> 116

Gly Ser Gly Thr Gln Leu Thr Val Leu
1 5

<210> 117
<211> 10
<212> PRT
<213> Homo sapiens

<400> 117

Gln Leu Thr Val Ile Ser Gln Pro Lys Ala
1 5 10

<210> 118
<211> 9
<212> PRT
<213> Homo sapiens

<400> 118

Ala Tyr Met Arg Glu His Asn Gln Leu
1 5

Claims

1. Agent for use in a method for therapy and/or prophylaxis of breast cancer and/or leukemia, wherein said agent comprises as an effective ingredient at least one polypeptide selected from the polypeptides (a) to (c) below, said polypeptide having an immunity-inducing activity/activities, or as an effective ingredient(s) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) and is/are capable of expressing said polypeptide(s) in vivo:

   (a) a polypeptide consisting of any one of the amino acid sequences shown in the odd number IDs of SEQ ID NOs:3 to 95;
   (b) a polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116 or SEQ ID NO:117; and
   c) a polypeptide comprising as a partial sequence thereof an amino acid sequence as shown in SEQ ID NO: 108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116 or SEQ ID NO:117, said polypeptide having 8 to 12 amino acid residues.

2. The agent for use according to claim 1, comprising more than one of said polypeptides as effective ingredients.

3. The agent for use according to claim 1 or claim 2, further comprising an immunoenhancer.

4. The agent for use according to any one of the preceding claims, wherein the method comprises administering to a patient the polypeptide or recombinant vector.

5. An isolated antigen-presenting cell for use in a method for therapy and/or prophylaxis of breast cancer and/or leukemia, said antigen-presenting cell comprising a complex between a polypeptide having an immunity-inducing activity as defined in claim 1 and an HLA molecule, optionally wherein the antigen presenting cell is a dendritic cell or a B cell.

6. An isolated T cell which selectively binds to a complex between a polypeptide having an immunity-inducing activity as defined in claim 1 and an HLA molecule for use in a method of therapy and/or prophylaxis of breast cancer and/or leukemia.

7. The antigen-presenting cell for use of claim 5 or the T cell for use of claim 6 wherein the method comprises administering to a patient the antigen-presenting cell and/or the T cell.

8. A method for detecting breast cancer and/or leukemia, which method is applied to a sample separated from a living body and comprises either:

   (1) measuring expression of at least one of the polypeptides (a) below:

      (a) a polypeptide produced in the living body and having a reactivity to bind, by antigen-antibody reaction, to an antibody against a polypeptide consisting of any one of the amino acid sequences shown in the odd

number IDs of SEQ ID NOs:3 to 95; (or

(2) investigation of expression of the CD179b gene having a coding region having any one of the nucleic acid sequences shown in SEQ ID NO:1 and the even number IDs of SEQ ID NOs:4 to 94 in a sample derived from a cancer patient, and comparison thereof with the expression level of the gene in a sample derived from a healthy individual.

9. The method according to claim 8, wherein the measurement of expression of said polypeptide(s) is carried out by measuring an antibody/antibodies which may be contained in the sample by immunoassay, which antibody/antibodies was/were induced in the living body against said polypeptide(s) to be measured.

10. A reagent for use in an *in vivo* method for detecting a breast cancer and/or leukemia, said reagent comprising a polypeptide which undergoes antigen-antibody reaction with an antibody induced in a living body against the polypeptide below:

(a) a polypeptide consisting of any one of the amino acid sequences shown in the odd number IDs of SEQ ID NOs:3 to 95.

11. *In vitro* use of a reagent for detecting a breast cancer and/or leukemia, said reagent comprising a polypeptide (a) below:

(a) a polypeptide consisting of amino acids in any one of the amino acid sequences shown in the odd number IDs of SEQ ID NOs:3 to 95.

Patentansprüche

1. Mittel zur Verwendung in einem Verfahren zur Therapie und/oder Prophylaxe von Brustkrebs und/oder Leukämie, wobei das Mittel als Wirkbestandteil zumindest ein Polypeptid umfasst, das aus den nachstehenden Polypeptiden (a) bis (c) ausgewählt ist, wobei das Polypeptid (eine) Immunität induzierende Aktivität(en) aufweist, oder als (einen) Wirkbestandteil(e) (einen) rekombinant(e) Vektor(en) umfasst, der/die (ein) Polynucleotid(e) umfasst/umfassen, das/die für das/die Polypeptid(e) kodiert/kodieren, und zur Expression des/der Polypeptids/Polypeptide in vivo in der Lage ist/sind:

(a) Polypeptid, das aus einer der Aminosäuresequenzen mit den ungeraden ID-Nummern der Seq.-ID Nr. 3 bis 95 besteht;
(b) Polypeptid, das aus der Aminosäuresequenz der Seq.-ID Nr. 108, Seq.-ID Nr. 109, Seq.-ID Nr. 110, Seq.-ID Nr. 111, Seq.-ID Nr. 112, Seq.-ID Nr. 113, Seq.-ID Nr. 114, Seq.-ID Nr. 115, Seq.-ID Nr. 116 oder Seq.-ID Nr. 117 besteht; und
(c) Polypeptid, das als Teilsequenz davon eine Aminosäuresequenz wie in Seq.-ID Nr. 108, Seq.-ID Nr. 109, Seq.-ID Nr. 110, Seq.-ID Nr. 111, Seq.-ID Nr. 112, Seq.-ID Nr. 113, Seq.-ID Nr. 114, Seq.-ID Nr. 115, Seq.-ID Nr. 116 oder Seq.-ID Nr. 117 dargestellt umfasst, wobei das Polypeptid 8 bis 12 Aminosäurereste aufweist.

2. Mittel zur Verwendung nach Anspruch 1, das mehr als eines der Polypeptide als Wirkbestandteile umfasst.

3. Mittel zur Verwendung nach Anspruch 1 oder Anspruch 2, das außerdem einen Immunverstärker umfasst.

4. Mittel zur Verwendung nach einem der vorangegangenen Ansprüche, wobei das Verfahren die Verabreichung des Polypeptids oder rekombinanten Vektors an einen Patienten umfasst.

5. Isolierte antigenpräsentierende Zelle zur Verwendung in einem Verfahren zur Therapie und/oder Prophylaxe von Brustkrebs und/oder Leukämie, wobei die antigenpräsentierende Zelle einen Komplex aus einem Polypeptid mit Immunität induzierender Aktivität nach Anspruch 1 und einem HLA-Molekül umfasst, wobei die antigenpräsentierende Zelle gegebenenfalls eine dendritische Zelle oder eine B-Zelle ist.

6. Isolierte T-Zelle, die selektiv an einen Komplex aus einem Polypeptid mit Immunität induzierender Aktivität nach Anspruch 1 und einem HLA-Molekül bindet, zur Verwendung in einem Verfahren zur Therapie und/oder Prophylaxe von Brustkrebs und/oder Leukämie.

7. Antigenpräsentierende Zelle zur Verwendung nach Anspruch 5 oder T-Zelle zur Verwendung nach Anspruch 6, wobei das Verfahren die Verabreichung der antigenpräsentierenden Zelle und/oder der T-Zelle an einen Patienten umfasst.

8. Verfahren zum Nachweis von Brustkrebs und/oder Leukämie, wobei das Verfahren an einer Probe angewandt wird, die aus einem lebenden Körper stammt, und eines der Folgenden umfasst:

(1) Messen der Expression von zumindest einem der nachstehenden Polypeptide (a):

(a) Polypeptid, das im lebenden Körper produziert wird und eine Reaktivität aufweist, um durch Antigen-Antikörper-Reaktion an einen Antikörper gegen ein Polypeptid zu binden, das aus einer beliebigen der Aminosäuresequenzen mit den ungeraden ID-Nummern der Seq.-ID Nr. 3 bis 95 besteht; oder

(2) Untersuchen der Expression des CD179b-Gens, das eine kodierende Region mit einer der in Seq.-ID Nr. 1 und den geradzahligen ID-Nummern der Seq.-ID Nr. 4 bis 94 dargestellten Nucleinsäuren aufweist, in einer Probe, die von einem Krebspatienten stammt, und ihr Vergleichen mit dem Expressionsniveau des Gens in einer Probe, die von einem gesunden Individuum stammt.

9. Verfahren nach Anspruch 8, wobei das Messen der Expression des/der Polypeptids/Polypeptide durch Messen eines/der Antikörper(s), der/die in der Probe enthalten sein kann/können, durch einen Immunoassay ausgeführt wird, wobei der/die Antikörper im lebenden Körper gegen das/die Polypeptid(e) induziert wurde(n), das/die gemessen werden soll(en).

10. Reagens zur Verwendung in einem In-vivo-Verfahren zum Nachweis von Brustkrebs und/oder Leukämie, wobei das Reagens ein Polypeptid umfasst, das eine Antigen-Antikörper-Reaktion mit einem Antikörper durchläuft, der in einem lebenden Körper gegen das nachstehende Polypeptid induziert wird:

(a) Polypeptid, das aus einer der Aminosäuresequenzen mit den ungeraden ID-Nummern der Seq.-ID Nr. 3 bis 95 besteht.

11. In-vitro-Verwendung eines Reagens zum Nachweis von Brustkrebs und/oder Leukämie, wobei das Reagens ein nachstehendes Polypeptid (a) umfasst:

(a) Polypeptid, das aus Aminosäuren in einer beliebigen der Aminosäuresequenzen mit den ungeraden ID-Nummern der Seq.-ID Nr. 3 bis 95 besteht.

Revendications

1. Agent à utiliser dans un procédé de thérapie et/ou de prophylaxie du cancer du sein et/ou de la leucémie, dans lequel ledit agent comprend comme ingrédient actif au moins un polypeptide choisi parmi les polypeptides (a) à (c) ci-dessous, ledit polypeptide ayant une activité/des activités induisant une immunité, ou comme ingrédient(s) actif(s) un ou des vecteurs recombinants comprenant un ou des polynucléotides codant pour ledit ou lesdits polypeptides et qui est/sont capables d'exprimer ledit ou lesdits polypeptides In vivo :

(a) un polypeptide consistant en l'une quelconque des séquences d'acides aminés représentées dans le nombre impair de ID SEQ ID NO: 3 à 95 ;
(b) un polypeptide constitué de la séquence d'acides aminés représentée dans SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116 ou SEQ ID NO:117 ; et
(c) un polypeptide comprenant, en tant que séquence partielle de celui-ci, une séquence d'acides aminés telle que représentée dans SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116 ou SEQ ID NO:117, ledit polypeptide ayant 8 à 12 résidus d'acides aminés.

2. Agent à utiliser selon la revendication 1, comprenant plus d'un desdits polypeptides comme ingrédients actifs.

3. Agent à utiliser selon la revendication 1 ou la revendication 2, comprenant en outre un stimulateur immunologique.

4. Agent à utiliser selon l'une quelconque des revendications précédentes, dans lequel le procédé comprend l'administration à un patient du polypeptide ou du vecteur recombinant.

5. Cellule présentant un antigène isolée à utiliser dans un procédé de thérapie et/ou de prophylaxie du cancer du sein et/ou de la leucémie, ladite cellule présentant un antigène comprenant un complexe entre un polypeptide ayant une activité induisant une immunité telle que définie dans la revendication 1 et une molécule de HLA, éventuellement dans laquelle la cellule présentant un antigène est une cellule dendritique ou une cellule B.

6. Cellule T isolée qui se lie sélectivement à un complexe entre un polypeptide ayant une activité induisant une immunité telle que définie à la revendication 1 et une molécule de HLA à utiliser dans un procédé de thérapie et/ou de prophylaxie du cancer du sein et/ou de la leucémie.

7. Cellule présentant un antigène isolé à utiliser selon la revendication 5 ou cellule T à utiliser selon la revendication 6, dans laquelle le procédé comprend l'administration à un patient de la cellule présentant un antigène et/ou de la cellule T.

8. Procédé de détection du cancer du sein et/ou de la leucémie, lequel procédé est appliqué à un échantillon séparé d'un corps vivant et comprend soit :

(1) la mesure de l'expression d'au moins l'un des polypeptides (a) ci-dessous :

(a) un polypeptide produit dans le corps vivant et ayant une réactivité pour se lier, par une réaction antigène-anticorps, à un anticorps contre un polypeptide consistant en l'une quelconque des séquences d'acides aminés représentées dans les ID de nombre impair de SEQ ID NO:3 à 95 ; ou

(2) une étude de l'expression du gène CD179b possédant une zone codante possédant l'une quelconque des séquences d'acide nucléique représentées dans SEQ ID NO:1 et des ID de nombre pair de SEQ ID NO:4 à 94 dans un échantillon provenant d'un patient cancéreux, et sa comparaison avec le niveau d'expression du gène dans un échantillon provenant d'un individu sain.

9. Procédé selon la revendication 8, dans lequel la mesure de l'expression dudit ou desdits polypeptides est réalisée en mesurant un anticorps/des anticorps pouvant être contenu(s) dans l'échantillon par immunodosage, lequel anticorps/lesquels anticorps ayant été induit(s) dans le corps vivant contre ledit ou lesdits polypeptides à mesurer.

10. Réactif à utiliser dans un procédé in vivo pour détecter un cancer du sein et/ou une leucémie, ledit réactif comprenant un polypeptide qui subit une réaction antigène-anticorps avec un anticorps induit dans un corps vivant contre le polypeptide ci-dessous :

(a) un polypeptide consistant en l'une quelconque des séquences d'acides aminés représentées dans les ID de nombre impair de SEQ ID NO:3 à 95.

11. Utilisation in vitro d'un réactif pour détecter un cancer du sein et/ou une leucémie, ledit réactif comprenant un polypeptide (a) ci-dessous :

(a) un polypeptide consistant en des acides aminés dans l'une quelconque des séquences d'acides aminés représentées dans les ID de numéro impair de SEQ ID NO:3 à 95.

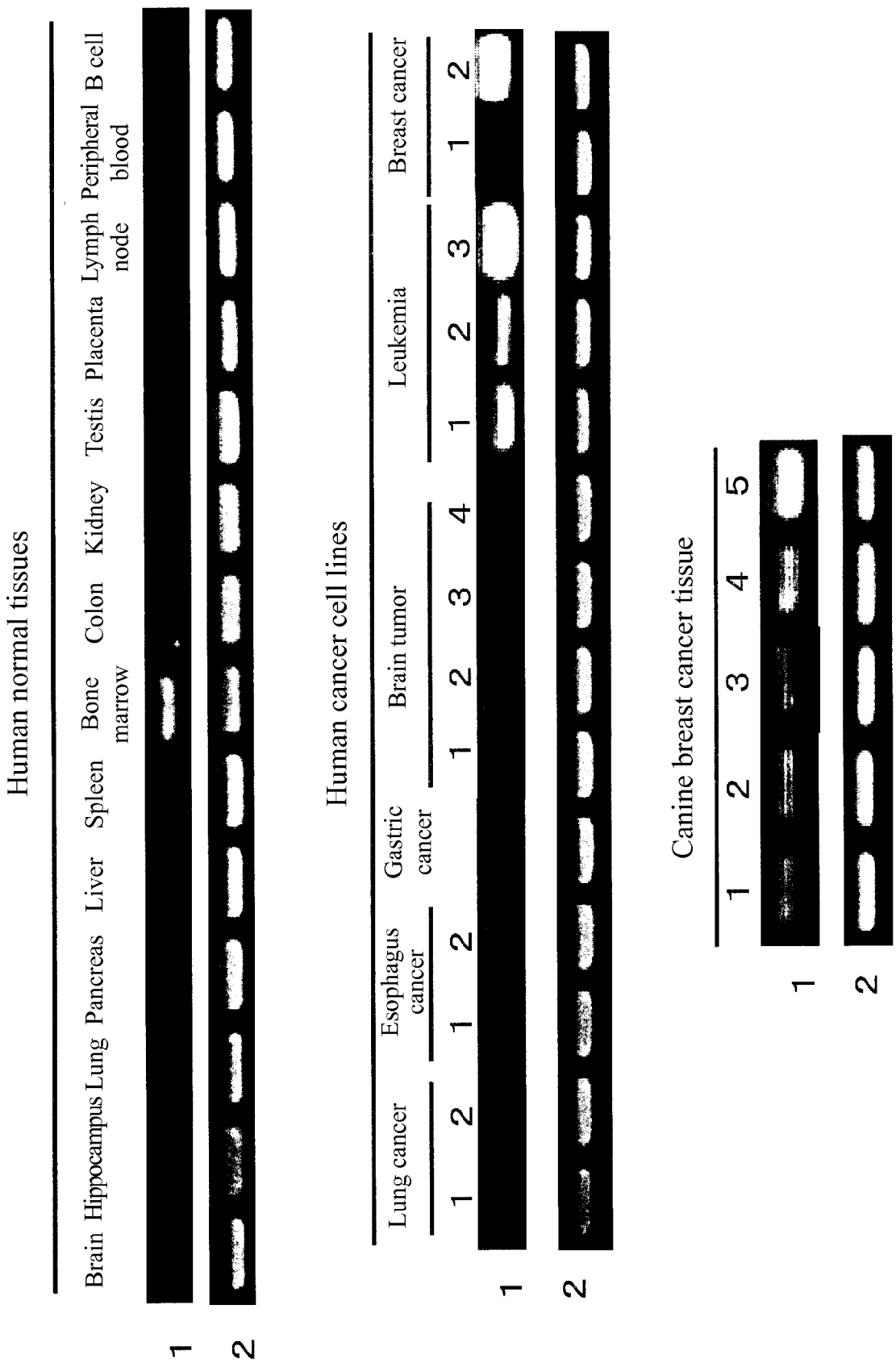
Human normal tissues
Brain
Hippocampus
Lung
Pancreas
Liver
Spleen
Bone marrow
Colon
Kidney
Testis
Placenta
Lymph node
Peripheral blood
B cell
1
2
Human cancer cell lines
Lung cancer
1
2
Esophagus cancer
1
2
Gastric cancer
Brain tumor
1
2
3
4
Leukemia
1
2
3
Breast cancer
1
2
1
2
Canine breast cancer tissue
1
2
3
4
5
1
2

Fig.1

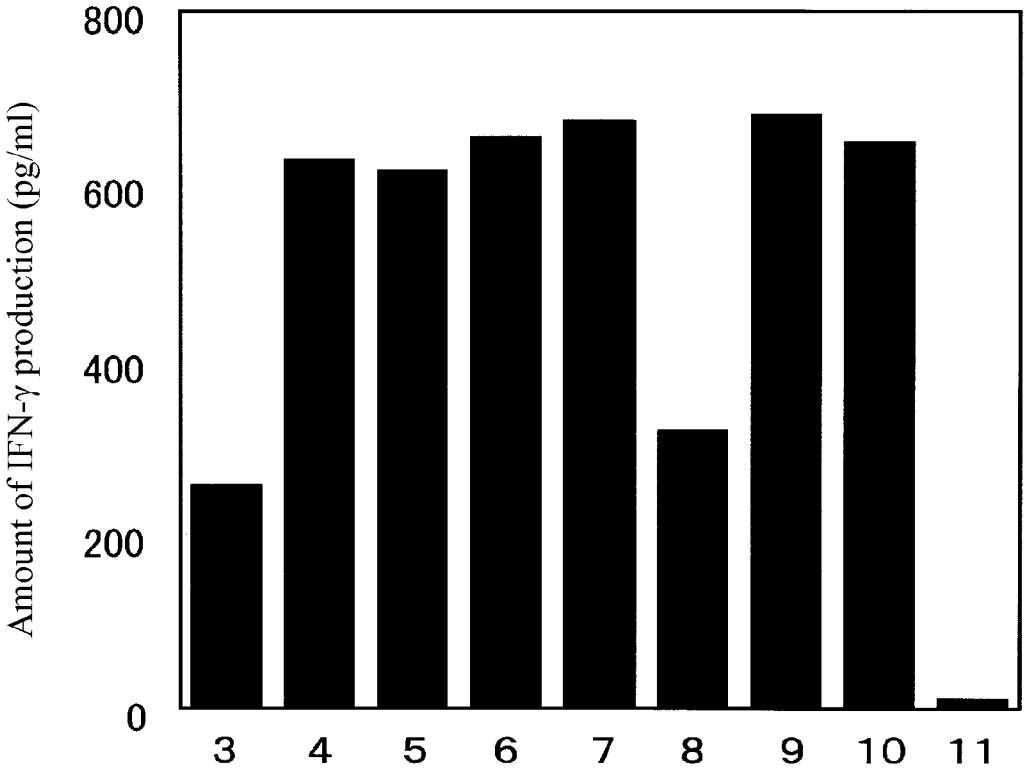
Amount of IFN-γ production (pg/ml)
800
600
400
200
0
3
4
5
6
7
8
9
10
11

Fig.2

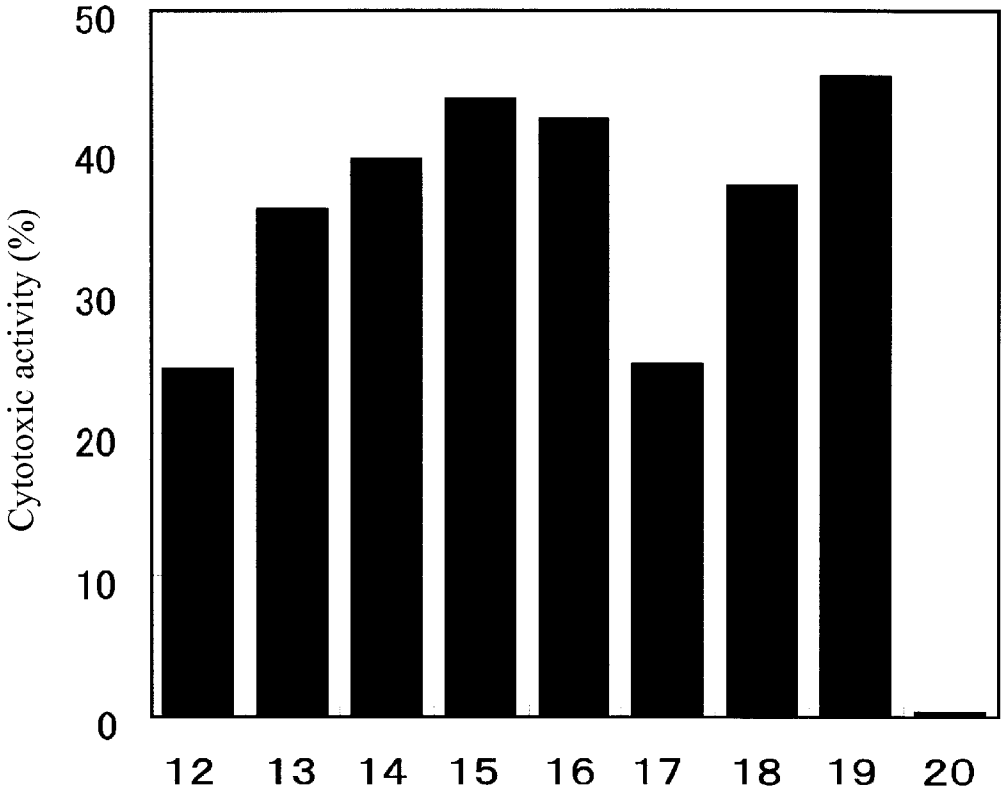
Cytotoxic activity (%)
50
40
30
20
10
0
12
13
14
15
16
17
18
19
20

Fig.3

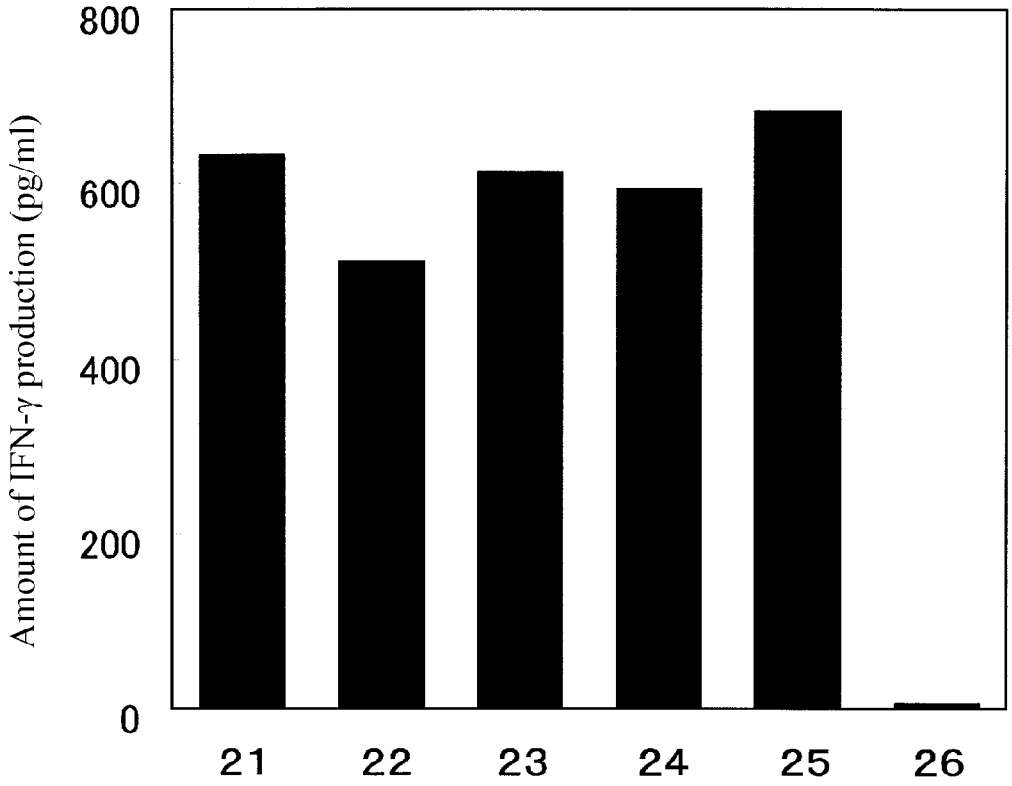
800
600
400
200
0
Amount of IFN-γ production (pg/ml)
21
22
23
24
25
26

Fig.4

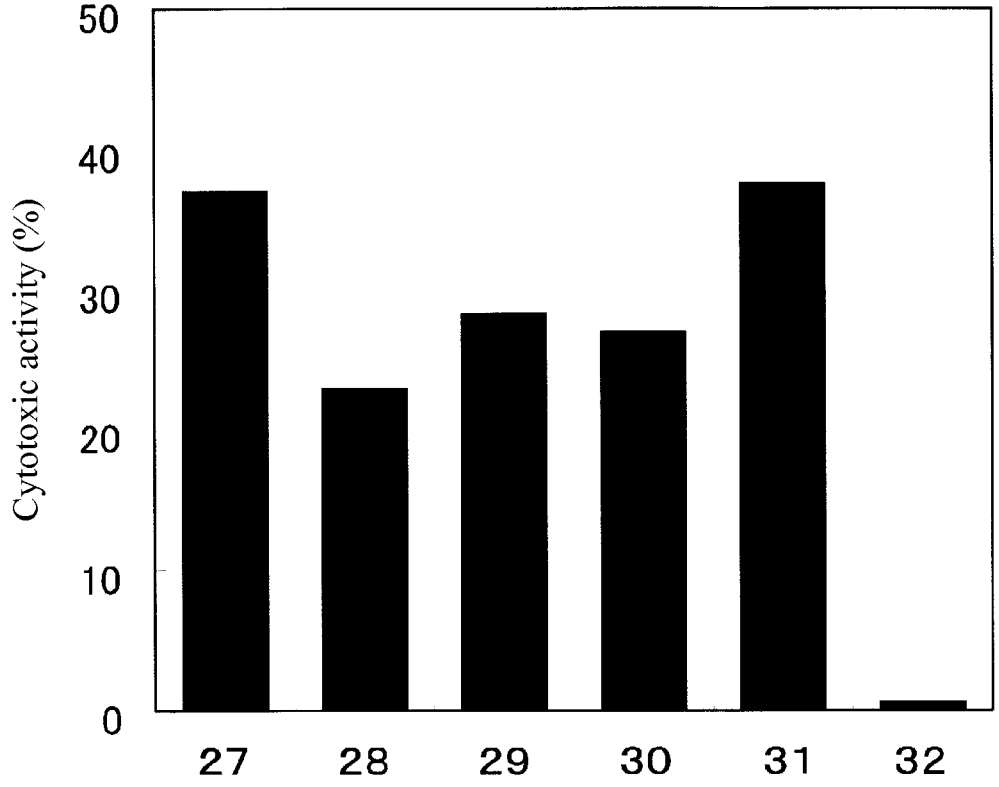
50
40
30
20
10
0
Cytotoxic activity (%)
27
28
29
30
31
32

Fig.5

REFERENCES CITED IN THE DESCRIPTION

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IMMUNITÁSINDUKÁLÓ ÁGENS ÉS ELJÁRÁS RÁK DETEKTÁLÁSÁRA

Szabadalmi igénypontok:

1. Ágens mellrák és/vagy leukémia kezelésére és/vagy megelőzésére szolgáló eljárásban történő alkalmazásra, ahol az ágens tartalmaz hatóanyagként legalább egy az alábbi (a)-(c) polipeptidek közül választott polipeptidet, amely polipeptid immunitásindukáló aktivitással/aktivitásokkal rendelkezik, vagy tartalmaz hatóanyag(ok)ként egy vagy több olyan rekombináns vektort, amely tartalmaz egy vagy több, a polipeptide(ke)t kódoló polinukleotidot és alkalmas a polipeptid(ek) *in vivo* expresszálásához:

   (a) a SEQ ID NO: 3-95 (azaz 3-95-ös azonosítási számú szekvenciák) közül a páratlan azonosítási számúakban bemutatott aminosav-szekvenciák bármelyikéből álló polipeptid;
   (b) a SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116 vagy SEQ ID NO: 117 által bemutatott aminosav-szekvencia bármelyikéből álló polipeptid; és
   (c) a SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116 vagy SEQ ID NO: 117 által bemutatott aminosav-szekvenciát parciális szekvenciaként tartalmazó polipeptid, amely polipeptid 8-12 aminosav-maradékkal rendelkezik.

2. Az ágens alkalmazásra az 1. igénypont szerint, amely több, mint egy említett polipeptidet tartalmaz hatóanyagokként.

3. Az ágens alkalmazásra az 1. vagy 2. igénypont szerint, amely tartalmaz továbbá immunitásfokozót.

4. Az ágens alkalmazásra az előző igénypontok bármelyike szerint, ahol az eljárás során beadjuk a polipeptidet vagy rekombináns vektort egy páciensnek.

5. Izolált antigénprezentáló sejt mellrák és/vagy leukémia kezelésére és/vagy megelőzésére szolgáló eljárásban történő alkalmazásra, az antigénprezentáló sejt tartalmazza egy 1. igénypontban definiált, immunitásindukáló aktivitással rendelkező polipeptid és HLA-molekula komplexét, ahol adott esetben az antigénprezentáló sejt dendritikus sejt vagy B-sejt.

6. Izolált T-sejt, amely szelektíven képes kötődni az 1. igénypontban definiált, immunitásindukáló aktivitással rendelkező polipeptid és HLA molekula egy komplexéhez mellrák és/vagy leukémia kezelésére és/vagy megelőzésére szolgáló eljárásban történő alkalmazásra.

7. Az antigénprezentáló sejt alkalmazásra az 5. igénypont szerint vagy a T-sejt alkalmazásra a 6. igénypont szerint, ahol az eljárás során beadjuk az antigénprezentáló sejtet és/vagy a T-sejtet egy páciensnek.

8. Eljárás mellrák és/vagy leukémia detektálására, amely eljárást élő testből vett mintán végezzük el, és amely eljárás során:

(1) megmérjük legalább egy, az alábbi (a) pont szerinti polipeptid expresszióját:

(a) az élő testben termelődő és a SEQ ID NO: 3-95 közül a páratlan azonosítási számúakban bemutatott aminosav-szekvenciák bármelyikéből álló polipeptid elleni egy antitesthez való, antigén-antitest reakció általi kötődésre vonatkozó reaktivitással rendelkező polipeptid; vagy

(2) vizsgáljuk a CD179b gén expresszióját, amely gén rendelkezik olyan kódoló régióval, amely rendelkezik a SEQ ID NO: 1 és a SEQ ID NO: 4-94 közül a páros azonosítási számúakban bemutatott nukleinsav-szekvenciák

bármelyikével, egy rákos pácienstől származó mintában, és összehasonlítjuk a génnek egy egészséges alanytól származó mintabeli expressziós szintjével.

9. A 8. igénypont szerinti eljárás, ahol a polipeptid(ek) expressziójának mérését úgy végezzük, hogy immuntesztvizsgálattal mérjük a mintában esetleg jelenlévő antitestet/antitesteket, amely antitest/antitestek az élő testben indukálódott/indukálódtak a mérendő polipeptid(ek) ellen.

10. Reagens mellrák és/vagy leukémia detektálására szolgáló *in vivo* eljárásban való alkalmazásra, amely reagens tartalmaz olyan polipeptidet, amely antigén-antitest reakción megy keresztül olyan antitesttel, amely élő testben indukálódott az alábbi polipeptid ellen:

(a) a SEQ ID NO: 3-95 közül a páratlan azonosítási számúakban bemutatott aminosav-szekvenciák bármelyikéből álló polipeptid.

11. Reagens *in vitro* alkalmazása mellrák és/vagy leukémia detektálására, amely reagens tartalmaz egy alábbi (a) polipeptidet:

(a) a SEQ ID NO: 3-95 közül a páratlan azonosítási számúakban bemutatott aminosav-szekvenciák egyikebeli aminosavakat tartalmazó polipeptid.