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(71) 出願人: 東レ株式会社 (TORAY INDUSTRIES, INC.) [JP/JP]; 〒1038666 東京都中央区日本橋室町2丁目1番1号 Tokyo (JP).

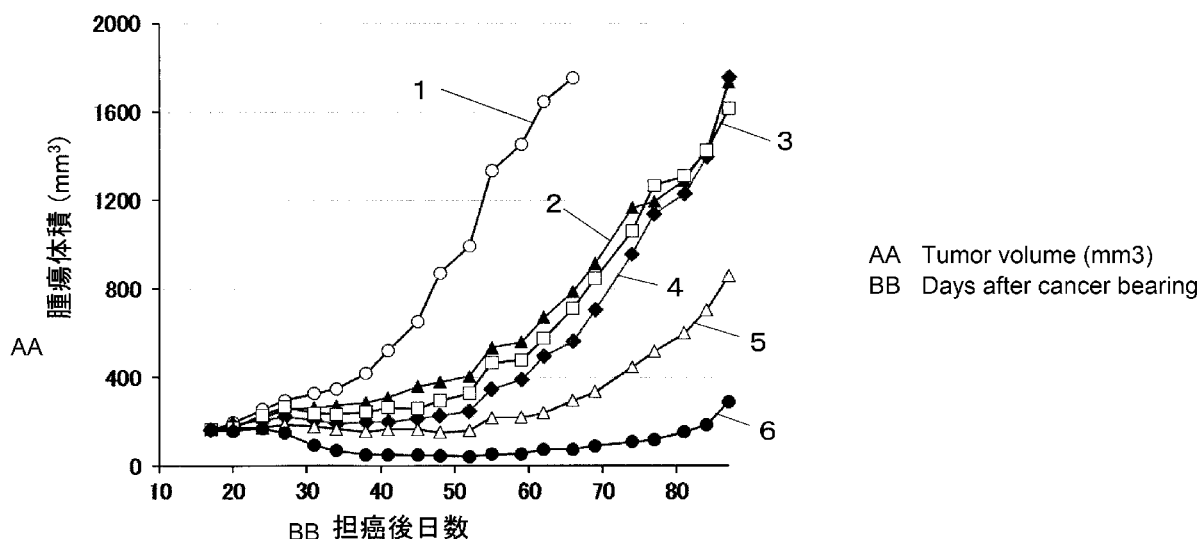
(72) 発明者: 岡野文義 (OKANO, Fumiyoshi); 〒2488555 神奈川県鎌倉市手広6丁目10番1号 東レ株式会社 基礎研究センター内 Kanagawa (JP). 赤澤大輔 (AKAZAWA, Daisuke); 〒2488555 神奈川県鎌倉市手広6丁目10番1号 東レ株式会社 基礎研究センター内 Kanagawa (JP).

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(54) Title: MEDICAMENT FOR TREATMENT AND/OR PREVENTION OF CANCER

(54) 発明の名称: 癌の治療及び／又は予防のための医薬品

【図1】



(57) Abstract: This medicament characterized by containing an antibody or a fragment thereof having an immunological reactivity with a CAPRIN-1 protein together or separately in combination with a pyrimidine drug, a platinum formulation, and an angiogenesis inhibitor is useful as a medicament for treatment and/or prevention of cancer in a cancer patient having a past history of another cancer treatment.

(57) 要約: CAPRIN-1タンパク質と免疫学的反応性を有する抗体又はそのフラグメントと、ピリミジン系薬剤、白金製剤及び血管新生阻害剤とを、一緒に又は別々に組み合わせて含むことを特徴とする医薬品は、他の癌治療の既往歴を有する癌患者の癌の治療及び／又は予防するための医薬品として有用である。

[続表有]

SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT,
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DESCRIPTION

Title of Invention: MEDICAMENT FOR TREATMENT AND/OR PREVENTION OF CANCER

Technical Field

[0001]

The present invention relates to a medicament for treatment and/or prevention of a cancer, comprising: an antibody against CAPRIN-1 protein, or a fragment thereof; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor.

Background Art

[0002]

Various antibody medicines targeting specific antigen proteins on cancer cells are applied as therapeutic agents for cancers with fewer side effects to cancer treatment because of their cancer specificity. For example, cytoplasmic-activation and proliferation-associated protein 1 (CAPRIN-1) is expressed on cell membrane surfaces of many solid cancers. Antibodies against this CAPRIN-1 protein are known to be promising in pharmaceutical uses for treatment and/or prevention of cancers (Patent Literature 1).

[0003]

In recent years, treatment methods using combinations of pluralities of therapeutic agents for cancer have been clinically used as standard treatment methods in order to enhance the effectiveness of the therapeutic agents for cancers. In general, for example, colon cancer is treated by a treatment method using a combination of irinotecan, folinic acid, and fluorouracil; breast cancer is treated by a treatment method using a combination of doxorubicin and cyclophosphamide or a combination of paclitaxel, trastuzumab, and pertuzumab; and gastric cancer is treated using a combination of anticancer agents such as carboplatin and fluorouracil. Therapeutic agents for cancers comprising anti-CAPRIN-1 antibodies as active ingredients have also been confirmed to have therapeutic effects on cancers by combinations with

chemotherapeutics (Patent Literature 2). However, treatment of a cancer by a combination of chemotherapeutics is not effective for every cancer to which the treatment is applied, and few combinations of chemotherapeutics synergistically drastically enhance therapeutic effects, though some combinations additively enhance therapeutic effects.

[0004]

One specific example of a cancer treatment method using a combination of a plurality of therapeutic agents for cancer is the combined use of a pyrimidine-based drug (for example, gemcitabine) and a platinum formulation (for example, carboplatin).

[0005]

The combined use of gemcitabine and carboplatin is also referred to as CBDCA+GEM, with which an attempt is being made to treat non-small-cell lung cancer, recurrent progressive ovarian cancer, urinary bladder cancer, breast cancer, (for example, triple-negative breast cancer), urothelial carcinoma, or the like.

[0006]

A breast cancer that is called TNBC [triple-negative breast cancer (a breast cancer which is negative for the HER2 protein, and negative for hormone receptors referred to as ER and PgR)] is one of the breast cancers on which the effects of an endocrine therapy and an anti-HER2 therapy cannot be expected, and which have a high malignancy and a high degree of therapeutic difficulty. In recent years, advancement in the analysis of gene expression profiles has facilitated the classification of TNBC. It has been reported that, administering carboplatin in a treatment in which docetaxel was administered to a Basal-like subtype of breast cancer (BLBC) having the highest frequency in TNBC after a treatment with epirubicin and cyclophosphamide (an EC treatment), was not effective (Non Patent Literature 1).

[0007]

Ovarian cancer is likely to metastasize into the abdominal cavity, the lymph node, the liver or the lung. In particular ovarian cancers progressing in Stage III or Stage IV, more than 50% of the cases recur within two years after the initial treatment, and thus, the cancer has an extremely high malignancy. For such a metastatic cancer primary to an ovarian cancer, a therapy with a combination of gemcitabine and carboplatin (GC) is used. In the case of a

patient whose PFI (Platinum-Free interval), interval from the termination of the initial chemotherapy to a recurrence, is six months or more (what is called a platinum-sensitive patient), the response rate of the treatment after the recurrence is 40% or more, but in the case of a patient whose PFI, interval from the termination of the chemotherapy to a recurrence, is less than six months (what is called a platinum-insensitive patient), the response rate of the treatment after the recurrence is 10% or less, which means an extremely poor prognosis (Non Patent Literature 2). As an intensification therapy for a platinum-sensitive ovarian cancer patient, a therapy with a combination of the three agents, namely, bevacizumab in addition to gemcitabine and carboplatin (GC-BEV) has been approved. As a result in a clinical trial, OCEANS, with a combination of the three agents, GC-BEV significantly extended the PFS (Progression-free Survival), compared with GC, but made no significant difference in the median value of the overall survival, OS (Non Patent Literature 3).

Citation List

Patent Literature

[0008]

Patent Literature 1: WO2010/016526

Patent Literature 2: WO2011/096535

Non Patent Literature

[0009]

Non Patent Literature 1: J Clin Oncol, 2012, 30, 1879-1887

Non Patent Literature 2: Crit Rev Oncol Hematol, 2007, 64, 129-138

Non Patent Literature 3: J Clin Oncol, 2012, 30, 2039-2045

Summary of Invention

Technical Problem

[0010]

An object of the present invention is to provide a medicament for treatment and/or prevention of a cancer specifically expressing CAPRIN-1 protein on a cell surface.

Solution to Problem

[0011]

As the result of intensive studies, the present inventors have found that a combined use (a combination) of four agents, namely, an antibody against CAPRIN-1 protein, or a fragment thereof, having an immunological reactivity with cancer cells, a pyrimidine-based drug (for example, gemcitabine), a platinum formulation (for example, carboplatin), and an angiogenesis inhibitor (for example, bevacizumab) exerts a remarkably stronger antitumor effect in a treatment than a combination of two agents, namely, a pyrimidine-based drug and a platinum formulation, or a combination of three agents, namely, an angiogenesis inhibitor in addition to the two agents, and furthermore exhibits an unpredictable increase in the antitumor effect, compared to the antitumor effect of a combination of three agents, namely, an antibody against CAPRIN-1 protein, or a fragment thereof, a pyrimidine-based drug, and a platinum formulation. On the basis of these findings, the present invention has been completed.

[0012]

Specifically, the present invention relates to the following embodiments (1) to (19).

[0013]

(1) A medicament for treatment and/or prevention of cancer, characterized by comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor, together or separately in combination, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor, together or separately in combination.

[0014]

(2) The medicament according to (1), wherein the cancer is a cancer in a cancer patient having a medical history of a cancer treatment with a pyrimidine-based drug and/or a platinum formulation.

[0015]

(3) The medicament according to (1) or (2), wherein the cancer is a cancer in a cancer patient for whom a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor together or separately in combination, was not effective.

[0016]

(4) The medicament according to any of (1) to (3), wherein the cancer is a cancer in a cancer patient for whom a cancer treatment with a pyrimidine-based drug and/or a platinum formulation was not effective.

[0017]

(5) The medicament according to any of (1) to (4), wherein the pyrimidine-based drug is gemcitabine and/or a derivative of gemcitabine.

[0018]

(6) The medicament according to any of (1) to (5), wherein the angiogenesis inhibitor is bevacizumab.

[0019]

(7) The medicament according to any of (1) to (6), wherein the platinum formulation is carboplatin, cisplatin, oxaliplatin, nedaplatin, and/or miriplatin.

[0020]

(8) The medicament according to any of (1) to (7), wherein the antibody or the fragment thereof has an immunological reactivity with CAPRIN-1 protein having an amino acid sequence shown by any one of the even numbered SEQ ID NOs among SEQ ID NOs: 2 to 30, or an amino acid sequence having 80% or more sequence identity with the amino acid sequence.

[0021]

(9) The medicament according to any of (1) to (8), wherein the antibody or the fragment thereof has an immunological reactivity with an extracellular region of CAPRIN-1 protein present on a cancer cell surface.

[0022]

(10) The medicament according to any of (1) to (9), wherein the antibody or the fragment thereof has an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having an amino acid sequence represented by any one of SEQ ID NOs: 31 to 35, 296 to 299, 308 and 309, or an amino acid sequence having 80% or more sequence identity with the amino acid sequence.

[0023]

(11) The medicament according to any of (1) to (10), wherein the antibody is a monoclonal antibody or a polyclonal antibody.

[0024]

(12) The medicament according to any of (1) to (11), wherein the antibody or a fragment thereof is any one of the following (A) to (M):

(A) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 36, 37 and 38 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 40, 41 and 42 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(B) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 44, 45 and 46 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 48, 49 and 50 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(C) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 52, 53 and 54 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions

of SEQ ID NOs: 56, 57 and 58 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(D) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 60, 61 and 62 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 64, 65 and 66 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(E) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 170, 171 and 172 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 173, 174 and 175 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(F) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 176, 177 and 178 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 179, 180 and 181 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(G) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 182, 183 and 184 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 185, 186 and 187 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(H) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 188, 189 and 190 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 191, 192 and 193 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(I) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 146, 147 and 148 (CDR1, CDR2 and

CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 149, 150 and 151 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(J) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 272, 273 and 274 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 275, 276 and 277 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(K) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 290, 291 and 292 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 293, 294 and 295 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(L) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 301, 302 and 303 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 305, 306 and 307 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein; and

(M) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 134, 135 and 136 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 137, 138 and 139 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein.

[0025]

(13) The medicament according to any of (1) to (12), wherein the antibody or the fragment thereof is any one of the following (a) to (al):

(a) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 39 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 43;

- (b) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 47 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 51;
- (c) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 55 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 59;
- (d) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 63 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 67;
- (e) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 69;
- (f) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 70 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 71;
- (g) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 72 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 73;
- (h) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 74 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 75;
- (i) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 76 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 77;
- (j) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 78 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 79;

- (k) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 80 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 81;
- (l) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 82 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 83;
- (m) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 84 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 85;
- (n) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 86 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 87;
- (o) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 88 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 89;
- (p) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 90 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 91;
- (q) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 92 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 93;
- (r) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 94 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 95;
- (s) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 96 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 97;

- (t) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 98 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (u) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 100 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 101;
- (v) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 102 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 103;
- (w) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 104 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 105;
- (x) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 106 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 107;
- (y) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 108 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 109;
- (z) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 110 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 111;
- (aa) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 112 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 113;
- (ab) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 115;

- (ac) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 116 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 117;
- (ad) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 119;
- (ae) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 120 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 121;
- (af) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 122 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 123;
- (ag) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 124 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
- (ah) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 126 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 127;
- (ai) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 129;
- (aj) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 130 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 131;
- (ak) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 133; and

(al) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 300 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 304.

[0026]

(14) The medicament according to any of (1) to (13), wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody or a single chain antibody.

[0027]

(15) The medicament according to any of (1) to (14), wherein the cancer is a cancer expressing CAPRIN-1 protein on a cell membrane surface.

[0028]

(16) The medicament according to any of (1) to (15), wherein the cancer is ovarian cancer, bile duct cancer, breast cancer, kidney cancer, pancreatic cancer, colon cancer, melanoma, lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, gastric cancer, mesothelial cancer, colorectal cancer, esophageal cancer, gastroesophageal junction cancer, hepatocellular carcinoma, glioblastoma, urothelial carcinoma, urinary bladder cancer, uterus cancer, primary central nervous system lymphoma, primary testicular lymphoma, biliary tract cancer, brain tumor, prostate cancer, leukemia, lymphoma, liver cancer, sarcoma, fibrosarcoma, mastocytoma, adrenocortical carcinoma, Ewing's tumor, multiple myeloma, testicular cancer, thyroid cancer, basal cell carcinoma, Paget's disease, or skin cancer.

[0029]

(17) A drug efficacy increasing agent of a pharmaceutical composition for treatment and/or prevention of cancer, wherein the agent is characterized by comprising, as active ingredients, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, wherein the pharmaceutical composition comprises, as an active ingredient, an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with a medicament comprising: the antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; the pyrimidine-

based drug; the platinum formulation; and the angiogenesis inhibitor, together or separately in combination.

[0030]

(18) A drug efficacy increasing agent of a pharmaceutical composition for treatment and/or prevention of cancer, characterized by comprising, as an active ingredient, an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein, wherein the pharmaceutical composition comprises, as active ingredients, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with a medicament comprising: the antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; the pyrimidine-based drug; the platinum formulation; and the angiogenesis inhibitor, together or separately in combination.

[0031]

(19) A method for treating and/or preventing cancer, characterized by comprising administering: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; carboplatin; and an angiogenesis inhibitor, together or separately to a subject, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: the antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; the pyrimidine-based drug; the platinum formulation; and the angiogenesis inhibitor, together or separately in combination.

Advantageous Effects of Invention

[0032]

The combined use of an antibody against CAPRIN-1 protein, or a fragment thereof, and a drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, according to the present invention, exerts a stronger antitumor effect than an antibody against CAPRIN-1 protein alone and than an existing chemotherapeutic (a combination of a pyrimidine-based drug and a platinum formulation, and a combination of a pyrimidine-based

drug, a platinum formulation, and an angiogenesis inhibitor). Furthermore, the combined use of an antibody against CAPRIN-1 protein, or a fragment thereof, and a drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, according to the present invention, exhibits a stronger antitumor effect than a monotherapy with an antibody against CAPRIN-1 protein or than an existing anticancer agent therapy with a pyrimidine-based drug, carboplatin, and an angiogenesis inhibitor. Accordingly, a combined use of an antibody against CAPRIN-1 protein, or an antibody against a fragment thereof, with a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor is effective for treatment and/or prevention of cancer.

Brief Description of Drawing

[0033]

[Figure 1] Figure 1 is a graph illustrating an antitumor effect of a combined use of an anti-CAPRIN-1 antibody with gemcitabine, carboplatin, and bevacizumab on NOD-SCID mice in which a human cancer cell line BT474 that expresses CAPRIN-1 was transplanted. The sizes of tumors of the mice are shown with: Reference Number 1; the administration of PBS instead of a drug, Reference Number 2; the administration of a combination of gemcitabine and carboplatin, Reference Number 3; the administration of an anti-CAPRIN-1 antibody, Reference Number 4; the administration of a combination of gemcitabine, carboplatin, and bevacizumab, Reference Number 5; the administration of a combination of gemcitabine, carboplatin, and an anti-CAPRIN-1 antibody, and Reference Number 6; the administration of a combination of gemcitabine, carboplatin, bevacizumab, and an anti-CAPRIN-1 antibody.

Description of Embodiments

[0034]

The antitumor activity of the combined use of an antibody against CAPRIN-1 protein or a fragment thereof (hereinafter, generically referred to as an “anti-CAPRIN-1 antibody”) with a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor used in the present

invention, can be evaluated by examining *in vivo* the inhibition of tumor growth in a tumor-bearing animal as mentioned later.

[0035]

As used herein, the term “comprising together or separately in combination” means comprising a plurality of drugs in the form in which the drugs can be administered simultaneously or separately to a patient. The form may be, for example, in the form of what is called a mixed formulation in which a plurality of drugs are mixed, or may be in the form of what is called a kit formulation comprising a plurality of drugs as individual formulations.

[0036]

Such a kit formulation according to the present invention may be, for example, a kit formulation comprising: a formulation (or pharmaceutical composition) containing an anti-CAPRIN-1 antibody; and a formulation (or pharmaceutical composition) containing a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor. Furthermore, a kit formulation according to the present invention may comprise another formulation (another known antitumor agent) in addition to an anti-CAPRIN-1 antibody, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor.

[0037]

The term “combined use” or “in combination” described herein refers to simultaneous administration or administration in a predetermined interval of the anti-CAPRIN-1 antibody and of the pyrimidine-based drug, the platinum formulation, and the angiogenesis inhibitor, as independent active ingredients to the same organism. The interval may be simultaneous administration or may be 30 minutes later, 1 hour later, 3 hours later, 6 hours later, 12 hours later, 1 day later, 3 days later, 5 days later, 7 days later, 2 weeks later, 3 weeks later, or 4 weeks later. Any one of an anti-CAPRIN-1 antibody; and a drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor may be administered, when the antibody or the drug exhibits its activity *in vivo*. The anti-CAPRIN-1 antibody may be administered first, or the drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor may be administered first.

[0038]

The anti-CAPRIN-1 antibody according to the present invention may be a monoclonal antibody or a polyclonal antibody and is preferably a monoclonal antibody. The antibody of the present invention may be any type of antibody, as long as it can exhibit antitumor activity. The antibody is a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, or a non-human animal antibody.

[0039]

Subjects in need of treatment and/or prevention of cancer according to the present invention are mammals such as human, pet animals, livestock animals, or sport animals. The preferred subject is a human.

[0040]

Anti-CAPRIN-1 antibodies, medicaments comprising, as active ingredients, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, and methods for treating and/or preventing cancers, related to the present invention, will be explained below.

[0041]

<Anti-CAPRIN-1 antibody>

Among CAPRIN-1 proteins having an amino acid sequence shown by any one of the even numbered SEQ ID NOs among SEQ ID NOs: 2 to 30, which are specific examples of antigens having an immunological reactivity with the anti-CAPRIN-1 antibody used in the present invention, the amino acid sequences shown by SEQ ID NOs: 6, 8, 10, 12 and 14 are amino acid sequences of canine CAPRIN-1 proteins; the amino acid sequences shown by SEQ ID NOs: 2 and 4 are amino acid sequences of human CAPRIN-1 proteins; the amino acid sequence shown by SEQ ID NO: 16 is an amino acid sequence of a bovine CAPRIN-1 protein; the amino acid sequence shown by SEQ ID NO: 18 is an amino acid sequence of an equine CAPRIN-1 protein; the amino acid sequences shown by SEQ ID NOs: 20, 22, 24, 26, and 28 are amino acid sequences of mouse CAPRIN-1 proteins; and the amino acid sequence shown by SEQ ID NO: 30 is an amino acid sequence of a chicken CAPRIN-1 protein.

[0042]

The anti-CAPRIN-1 antibody used in the present invention may have an immunological reactivity with CAPRIN-1 protein variant having 80% or more, preferably 90% or more, more

preferably 95% or more, and further preferably 99% or more sequence identity to the amino acid sequence shown by any one of the even numbered SEQ ID NOs among SEQ ID NOs: 2 to 30. The term “% sequence identity” as used herein means a percentage (%) of the number of identical amino acids (or nucleotides) to the total number of amino acids (or nucleotides) in the case that two sequences are aligned such that maximum similarity can be achieved with or without introduction of gaps.

[0043]

In the present invention, the anti-CAPRIN-1 antibody refers to an antibody or a fragment thereof having an immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof (antigen binding fragment). The term “immunological reactivity” used herein indicates the characteristics of an antibody binding *in vivo* specifically to CAPRIN-1 protein or a partial polypeptide thereof.

[0044]

The anti-CAPRIN-1 antibody used in the present invention may be a monoclonal antibody or a polyclonal antibody.

[0045]

Polyclonal antibodies having an immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof (anti-CAPRIN-1 polyclonal antibodies) can be obtained, for example, in a manner described below. Serum is obtained from mice, human antibody-producing mice, rats, rabbits, chickens, or the like immunized with a naturally occurring CAPRIN-1 protein or a protein fused with GST or the like, or a partial peptide thereof. The obtained serum is purified via ammonium sulfate precipitation, protein A, protein G, DEAE ion-exchange columns, affinity columns to which CAPRIN-1 protein or a partial peptide is coupled, or the like.

[0046]

As for nucleotide sequences and amino acid sequences of CAPRIN-1 and homologs thereof used in the immunization can be obtained by, for example, accessing the website of GenBank (NCBI, USA) and using the BLAST or FASTA algorithm (Karlin and Altschul, Proc. Natl. Acad. Sci. USA, 90:5873-5877, 1993; and Altschul et al., Nucleic Acids Res. 25:3389-

3402, 1997). Methods for producing CAPRIN-1 protein can be obtained with reference to WO2014/012479 or may employ cells or the like expressing CAPRIN-1 protein.

[0047]

Monoclonal antibodies having an immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof (anti-CAPRIN-1 monoclonal antibodies) can be obtained, for example, in a manner described below. Breast cancer cells SK-BR-3 expressing CAPRIN-1, a full-length CAPRIN-1 protein or a fragment thereof, or the like is administered to mice for immunization. Splenocytes separated from the mice are fused with myeloma cells. Clones capable of producing anti-CAPRIN-1 monoclonal antibodies can be selected from the obtained fusion cells (hybridomas) to obtain these antibodies. The antibodies produced from the selected hybridomas can be obtained in the same way as the aforementioned method for purifying polyclonal antibodies.

[0048]

The antibody used in the present invention includes human antibodies, humanized antibodies, chimeric antibodies, and non-human animal antibodies.

[0049]

For human antibodies, human lymphocytes infected with EB virus are sensitized with a protein, protein-expressing cells, or a lysate thereof. The sensitized lymphocytes are fused with human-derived myeloma cells such as U266 cells. Antibodies having an immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof can be obtained from the obtained fusion cells.

[0050]

A humanized antibody is a modified antibody, and it is sometimes referred to as a reshaped human antibody. It is known that a humanized antibody is constructed by transplanting complementarity determining regions of an immunized animal-derived antibody into complementarity determining regions of a human antibody. In addition, a general gene recombinant technique therefor is well known. Specifically, a DNA sequence designed in a manner that allows complementarity determining regions of mouse or rabbit antibody to be ligated to human antibody framework regions is synthesized by the PCR method using several

oligonucleotides prepared in such a manner that the oligonucleotides have portions overlapping each other at one end of each thereof. A humanized antibody can be obtained by ligating the above obtained DNA to DNA encoding a human antibody constant region, incorporating the resultant into an expression vector, and introducing the vector into a host for antibody production (see EP-A-239400 and WO96/02576). Framework regions of human antibody ligated to each other via complementarity determining regions are selected on the assumption that complementarity determining regions can form a good antigen binding site. If necessary, amino acids in framework regions of an antibody variable region may be substituted in such a manner that complementarity determining regions in a reshaped human antibody form an appropriate antigen binding site (Sato K. et al., Cancer Research 1993, 53:851-856). In addition, the framework regions may be substituted with framework regions from a different human antibody (see WO99/51743).

[0051]

In general, antibodies are heteromultimeric glycoproteins each comprising at least two heavy chains and two light chains. Antibodies each comprise two identical light chains and two identical heavy chains. Each heavy chain has a heavy-chain variable region at one end thereof, to which some constant regions are bound in series. Each light chain has a light-chain variable region at one end thereof to which some constant regions are bound in series. Variable regions have a specific variable region, which is called complementarity determining region (CDR) and imparts binding specificity to an antibody. A relatively conserved portion in a variable region is called a framework region (FR). A complete heavy-chain or light-chain variable region comprises 4 FRs connected to each other via 3 CDRs (CDR1 to CDR3).

[0052]

Sequences of human-derived heavy-chain and light-chain constant regions and variable regions can be obtained from, for example, NCBI (USA; GenBank, UniGene, etc.). For example, for a human IgG1 heavy-chain constant region, see registration No. J00228; for a human IgG2 heavy-chain constant region, see registration No. J00230; for a human light chain κ constant region, see sequences such as registration Nos. V00557, X64135, and X64133; and

for a human light chain λ constant region, see sequences such as registration Nos. X64132 and X64134.

[0053]

A chimeric antibody is an antibody produced by combining sequences from different animals. An example thereof is an antibody composed of mouse antibody heavy-chain and light-chain variable regions and constant regions of human antibody heavy-chain and light-chain variable regions. Such a chimeric antibody can be produced by a known method. For example, it can be obtained by ligating DNA encoding an antibody V region to DNA encoding a human antibody C region, incorporating the resultant into an expression vector, and introducing the vector into a host for antibody production.

[0054]

Non-human animal antibodies are obtained by immunizing animals with sensitizing antigens according to a known method or by intraperitoneally, intracutaneously, or subcutaneously injecting sensitizing antigens into animals such as mice as a general method. For injecting sensitizing antigens, an appropriate amount of various adjuvants including CFA (Freund's complete adjuvant) is mixed therewith and the mixture is administered to animals several times. After immunization of animals and confirmation of an anti-CAPRIN-1 antibody contained in serum, the serum is obtained and the non-human animal antibody can be obtained by purification via ammonium sulfate precipitation, protein A, protein G, DEAE ion-exchange columns, affinity columns to which CAPRIN-1 protein or a partial peptide is coupled, or the like, as mentioned above. In the case of obtaining monoclonal antibodies from non-human animals, a monoclonal antibody is obtained by collecting immunocytes from the immunized animals and subjected to cell fusion with myeloma cells. The cell fusion of immunocytes with myeloma cells can be carried out according to a known method (see Kohler, G. and Milstein, C. *Methods Enzymol.* (1981) 73, 3-46).

[0055]

The antibody used in the present invention can also be obtained as a gene recombinant antibody produced by cloning an antibody gene from a hybridoma, incorporating the clone into an adequate vector, introducing the vector into a host, and producing the antibody by using a

gene recombinant technique (see Carl, A.K. Borrebaeck, James, W. Larrick, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990).

[0056]

Amino acids in a variable region (e.g., FR) or a constant region in the anti-CAPRIN-1 antibody used in the present invention may be substituted with different amino acids. The amino acid substitution is a substitution of 1 or several, for example, less than 15, less than 10, not more than 8, not more than 6, not more than 5, not more than 4, not more than 3, or not more than 2 amino acids, preferably 1 to 9 amino acids. A substituted antibody should have characteristics of specifically binding to the antigen and binding affinity for the antigen equivalent to or more than those of an unsubstituted antibody and should be an antibody that causes no rejection when applied to humans. The amino acid substitution is preferably a conservative amino acid substitution, which is a substitution between amino acids having similar characteristics in terms of charge, side chains, polarity, aromaticity, and the like. For example, characteristically similar amino acids can be classified into the following types: basic amino acids (arginine, lysine, and histidine); acidic amino acids (aspartic acid and glutamic acid); uncharged polar amino acids (glycine, asparagine, glutamine, serine, threonine, cysteine, and tyrosine); nonpolar amino acids (leucine, isoleucine, alanine, valine, proline, phenylalanine, tryptophan, and methionine); branched-chain amino acids (threonine, valine, isoleucine); and aromatic amino acids (phenylalanine, tyrosine, tryptophan, and histidine).

[0057]

The anti-CAPRIN-1 antibody used in the present invention is expected to have a stronger antitumor effect when having higher binding affinity for CAPRIN-1 protein on cancer cell surfaces. Association constant (affinity constant) K_a (k_{on}/k_{off}) is preferably at least $10^7 M^{-1}$, at least $10^8 M^{-1}$, at least $5 \times 10^8 M^{-1}$, at least $10^9 M^{-1}$, at least $5 \times 10^9 M^{-1}$, at least $10^{10} M^{-1}$, at least $5 \times 10^{10} M^{-1}$, at least $10^{11} M^{-1}$, at least $5 \times 10^{11} M^{-1}$, at least $10^{12} M^{-1}$, or at least $10^{13} M^{-1}$.

[0058]

The anti-CAPRIN-1 antibody used in the present invention may be chemically modified. Examples of such an antibody modifier can include antibodies bound to various molecules such

as polyethylene glycol (PEG) and antitumor compounds (for example, antitumor agents listed below). Regarding antibody modifiers of the present invention, substances that bind to an antibody are not limited. Such an antibody modifier can be obtained by chemically modifying an obtained antibody. Methods of such modification have been already established in the field related to the present invention.

[0059]

The binding strength of the anti-CAPRIN-1 antibody used in the present invention against effector cells can be improved by substituting 1, 2 or several amino acids in the heavy chain-constant region of the antibody or by removing fucose bound to *N*-acetylglucosamine in an *N*-glycoside-linked sugar chain bound to the heavy-chain constant region. The anti-CAPRIN-1 antibody described above may have the amino acid substitution alone or may be a composition with an antibody bound to fucose.

[0060]

Antibodies in which 1, 2 or several amino acids in the heavy-chain constant region have been substituted can be produced with reference to, for example, WO2004/063351, WO2011/120135, U.S. Patent No. 8388955, WO2011/005481, U.S. Patent No. 6737056, and WO2005/063351.

[0061]

Antibodies in which fucose bound to *N*-acetylglucosamine in an *N*-glycoside-linked sugar chain in the heavy-chain constant region has been removed, or producing cells thereof can be produced with reference to U.S. Patent No. 6602684, EP Patent No. 1914244, and U.S. Patent No. 7579170. Compositions or producing cells of antibodies in which fucose bound to *N*-acetylglucosamine in an *N*-glycoside-linked sugar chain bound to the heavy-chain constant region has been removed, with antibodies bound to fucose can be produced with reference to, for example, U.S. Patent No. 8642292.

[0062]

The anti-CAPRIN-1 polyclonal antibody and the anti-CAPRIN-1 monoclonal antibody used in the present invention, methods for producing or purifying antibodies and methods for producing CAPRIN-1 protein or partial polypeptide thereof used in immunization can be

obtained with reference to WO2010/016526, WO2011/096517, WO2011/096528, WO2011/096519, WO2011/096533, WO2011/096534, WO2011/096535, WO2013/018886, WO2013/018894, WO2013/018892, WO2013/018891, WO2013/018889, WO2013/018883, WO2013/125636, WO2013/125654, WO2013/125630, WO2013/125640, WO2013/147169, WO2013/147176 and WO2015/020212.

[0063]

Specific examples of the anti-CAPRIN-1 antibody according to the present invention include anti-CAPRIN-1 antibodies described in WO2010/016526, WO2011/096517, WO2011/096528, WO2011/096519, WO2011/096533, WO2011/096534, WO2011/096535, WO2013/018886, WO2013/018894, WO2013/018892, WO2013/018891, WO2013/018889, WO2013/018883, WO2013/125636, WO2013/125654, WO2013/125630, WO2013/125640, WO2013/147169, WO2013/147176 and WO2015/020212 mentioned above. Preferred examples of the anti-CAPRIN-1 antibody include the following.

[0064]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein having the amino acid sequence shown by SEQ ID NO: 2 or SEQ ID NO: 4 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more, and still further preferably 99% or more) sequence identity to the amino acid sequence.

[0065]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 31 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 36, 37 and 38 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 40, 41 and 42 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein; an antibody or

a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 140, 141 and 142 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 143, 144 and 145 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein; or an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 164, 165 and 166 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 167, 168 and 169 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 39 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 43; an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 70 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 71; or an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 78 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 79.

[0066]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 33 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 60, 61 and 62 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 64, 65 and 66 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region

comprising the amino acid sequence of SEQ ID NO: 63 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 67.

[0067]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 32 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 52, 53 and 54 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 56, 57 and 58 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 55 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 59.

[0068]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 34 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 170, 171 and 172 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 173, 174 and 175 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein; or an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 176, 177 and 178 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 179, 180 and 181 (CDR1, CDR2 and CDR3, respectively),

and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 80 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 81; or an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 82 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 83.

[0069]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 35 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 182, 183 and 184 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 185, 186 and 187 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein; or an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 188, 189 and 190 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 191, 192 and 193 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 84 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 85; or an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 86 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 87.

[0070]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 44, 45 and 46 (CDR1, CDR2 and CDR3,

respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 48, 49 and 50 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 47 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 51.

[0071]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 296 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 146, 147 and 148 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 149, 150 and 151 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 72 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 73.

[0072]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 297 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 272, 273 and 274 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 275, 276 and 277 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1

protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 115.

[0073]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 298 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 290, 291 and 292 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 293, 294 and 295 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 120 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 121.

[0074]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 299 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 301, 302 and 303 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 305, 306 and 307 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 300 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 304.

[0075]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 308 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 134, 135 and 136 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 137, 138 and 139 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 69.

[0076]

An antibody or a fragment thereof having an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having the amino acid sequence shown by SEQ ID NO: 309 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, and further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 134, 135 and 136 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 137, 138 and 139 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein. More preferably, an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 69.

[0077]

In addition, the following anti-CAPRIN-1 antibodies are preferably used.

[0078]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 69.

[0079]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 70 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 71.

[0080]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 72 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 73.

[0081]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 74 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 75.

[0082]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 76 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 77.

[0083]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 78 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 79.

[0084]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 80 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 81.

[0085]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 82 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 83.

[0086]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 84 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 85.

[0087]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 86 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 87.

[0088]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 88 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 89.

[0089]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 90 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 91.

[0090]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 92 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 93.

[0091]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 94 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 95.

[0092]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 96 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 97.

[0093]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 98 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 99.

[0094]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 100 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 101.

[0095]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 102 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 103.

[0096]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 104 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 105.

[0097]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 106 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 107.

[0098]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 108 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 109.

[0099]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 110 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 111.

[0100]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 112 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 113.

[0101]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 115.

[0102]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 116 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 117.

[0103]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 119.

[0104]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 120 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 121.

[0105]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 122 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 123.

[0106]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 124 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 125.

[0107]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 126 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 127.

[0108]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 129.

[0109]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 130 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 131.

[0110]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 133.

[0111]

An antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 300 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 304.

[0112]

In Examples mentioned later, a polyclonal antibody or a monoclonal antibody against full-length CAPRIN-1 protein or a polypeptide of a portion of a region expressed on cell membrane surfaces of cancer cells, combined with a drug comprising a pyrimidine-based drug and a platinum formulation, was confirmed to have its strong antitumor effect in cancer-bearing organisms.

[0113]

<Pyrimidine-based Drug>

The pyrimidine-based drug includes fluorouracil (5-FU) or tegafur (FT) that is a prodrug of fluorouracil; xifluridine, doxifluridine, a cytarabine formulation, or derivatives thereof; and preferably gemcitabine and/or derivatives of gemcitabine.

[0114]

<Platinum Formulation>

The platinum formulation is a metal complex in which the central metal is composed of platinum, four ligands are on the same plane, and an amine as one of the ligands forms a cis form. The platinum formulation is a drug that exerts an antitumor effect when coordinated to a guanine base of a DNA, and may comprise a suitable isotonicizing agent or pH or a suitable dosage form to be administered to an organism. Specific examples of the platinum formulation include carboplatin, cisplatin, oxaliplatin, nedaplatin, and miriplatin, and preferably carboplatin.

[0115]

<Angiogenesis inhibitor>

The angiogenesis inhibitor is a drug that inhibits the migration and growth of a vascular endothelial cell, and inhibits angiogenesis, and is preferably an anti-VEGF inhibitor and/or an anti-vascular endothelial growth factor receptor (VEGFR) inhibitor. Specific examples of the anti-VEGF inhibitor include Bevacizumab, Ranibizumab, Lenvatinib mesilate, and Ziv-Aflibercept, and specific examples of the anti-vascular endothelial growth factor receptor (VEGFR) inhibitor include Ramucirumab, Axitinib, Cabozantinib, Regorafenib, Sorafenib, Sunitinib, Vandetanib, and Pazopanib. Bevacizumab is preferable.

[0116]

<Another Drug>

As active ingredients of a medicament according to the present invention, the anti-CAPRIN-1 antibody and the drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor may be used in combination with an antitumor agent known in literature, etc. Specific examples of known antitumor agents include, but are not particularly limited to, paclitaxel, nab-paclitaxel, doxorubicin, daunorubicin, cyclophosphamide,

methotrexate, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylolomelamine, bullatacin, bullatacinone, camptothecin, bryostatin, callystatin, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chloRNAphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, dynemicin, clodronate, esperamicin, aclacinomycin, actinomycin, authramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophilin, chromomycin, dactinomycin, detorbicin, 6-diazo-5-oxo-L-norleucine, adriamycin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycin, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmo fur, dideoxyuridine, enocitabine, floxuridine; androgens, for example, calusterone, dromostanolone propionate, epitiostanol, mepitiothane, testolactone, aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone, aldophosphamide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, lentinan, lonidamine, maytansine, ansamitocine, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, schizophyllan, spirogermanium, tenuazonic acid, triaziquone, roridine A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, docetaxel, chlorambucil, 6-thioguanine, mercaptopurine, vinblastine, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, irinotecan, topoisomerase inhibitor, difluoromethylornithine (DMFO), retinoic acid, and pharmacologically acceptable (known) salts or (known) derivatives thereof.

[0117]

<Antitumor effect of present invention>

The combination of the anti-CAPRIN-1 antibody with a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, according to the present invention, has cytotoxic activity *in vivo*. Accordingly, the antitumor effect of the present invention can be determined by examining cytotoxic activity against cancer. The cytotoxic activity can be evaluated by administering the anti-CAPRIN-1 antibody and the drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor to an organism having cancer, measuring the size of a tumor after the administration, and examining the size of the cancer over time. Also, the antitumor effect of the present invention can be evaluated by examining a survival rate. Alternatively, the antitumor effect of the present invention may be evaluated by examining the ability to produce cytokines or chemokines. The antitumor effect of the combination of the anti-CAPRIN-1 antibody with the drug comprising a drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor according to the present invention can be further determined by examining prevention of cancer, prevention of metastasis or prevention of recurrence.

[0118]

The anti-CAPRIN-1 antibody used in the present invention can be expected to have a stronger antitumor effect when having higher binding affinity for CAPRIN-1 protein on cancer cell surfaces. Association constant (affinity constant) K_a (k_{on}/k_{off}) is preferably at least $10^7 M^{-1}$, at least $10^8 M^{-1}$, at least $5 \times 10^8 M^{-1}$, at least $10^9 M^{-1}$, at least $5 \times 10^9 M^{-1}$, at least $10^{10} M^{-1}$, at least $5 \times 10^{10} M^{-1}$, at least $10^{11} M^{-1}$, at least $5 \times 10^{11} M^{-1}$, at least $10^{12} M^{-1}$, or at least $10^{13} M^{-1}$.

[0119]

An ability of an anti-CAPRIN-1 antibody used in the present invention to bind to CAPRIN-1 can be determined via binding assay using, for example, ELISA, a Western blot method, immunofluorescence, or flowcytometry analysis.

[0120]

Administering, to an organism having cancer, a combination of an anti-CAPRIN-1 antibody with a drug comprising a pyrimidine-based drug, a platinum formulation, and an

angiogenesis inhibitor, according to the present invention, increases an antitumor effect as compared with an anti-CAPRIN-1 antibody alone, as mentioned above. The rate of increase is preferably 30% or more, more preferably 40% or more, further preferably 50% or more, still further preferably 55% or more, even further preferably 60% or more, even further preferably 65% or more, and most preferably 70% or more. The rate of increase in antitumor effect by administration of a combination of an anti-CAPRIN-1 antibody with a drug comprising a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, according to the present invention, with respect to administration of the anti-CAPRIN-1 antibody alone can be calculated by administering their respective effective amounts to cancer-bearing mice under the same conditions, and comparing tumor volumes on 7 days or later after the start of administration.

[0121]

<Medicament for treatment and/or prevention of cancer>

A medicament of the present invention is aimed at treating and/or preventing cancer. A cancer targeted by the medicament of the present invention is not particularly limited as long as it is a cancer (cells) expressing CAPRIN-1 protein.

[0122]

The term “treatment” used herein refers to treatment of cancer based on an antitumor effect mentioned above. The term “prevention” used herein refers to not only prevention of development of cancer but prevention of metastasis or recurrence of cancer.

[0123]

Both the terms “tumor” and “cancer” used herein refer to malignant neoplasm, and thus they are used in an exchangeable manner.

[0124]

In the present invention, a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, together or separately in combination, may be a cancer patient who had a cancer treatment with a medicament other than

such a combination, and also encompasses a patient who was treated with a chemotherapeutic, a molecular target drug, or a hormone therapy in the past. Examples include a cancer patient who had a cancer treatment in accordance with “NCCN Clinical Practice Guidelines in Oncology”, “ESMO Clinical Practice Guidelines”, or “Clinical Practice Guideline on Cancer”. The cancer patient preferably has a medical history of a cancer treatment with a platinum formulation. The cancer patient preferably has a medical history of a cancer treatment with a pyrimidine-based drug and/or a platinum formulation (specific examples include carboplatin, cisplatin, oxaliplatin, and nedaplatin).

[0125]

In addition, the cancer patient having a medical history is preferably a cancer patient for whom a cancer treatment with a medicament other than a cancer treatment with a medicament comprising: an anti-CAPRIN-1 antibody, a pyrimidine-based drug, and a platinum formulation, together or separately in combination, was not effective, more preferably a cancer patient for whom a cancer treatment with a pyrimidine-based drug and/or a platinum formulation was not effective.

[0126]

In addition, the cancer patient having a medical history is preferably a cancer patient having a cancer resistant to a cancer treatment with a medicament other than a cancer treatment with a medicament comprising an anti-CAPRIN-1 antibody, a pyrimidine-based drug, and a platinum formulation together or separately in combination, still more preferably a cancer patient having a cancer resistant to a cancer treatment with a pyrimidine-based drug and/or a platinum formulation. Here, the expressions “a cancer treatment was not effective” and “resistant to a cancer treatment” were used synonymously.

[0127]

Cancer that can be a target in the present invention is any cancer as long as the cancer expresses CAPRIN-1 protein on a cell membrane surface. The cancer is preferably ovarian cancer, bile duct cancer, breast cancer, kidney cancer, pancreatic cancer, colon cancer, melanoma (including postoperative melanoma), lung cancer (including non-small-cell lung cancer and small cell lung cancer), renal cell carcinoma, Hodgkin’s lymphoma, head and neck

cancer, gastric cancer, mesothelial cancer (including malignant pleural mesothelioma), colorectal cancer (for example, colorectal cancer having MSI-high), esophageal cancer, gastroesophageal junction cancer, hepatocellular carcinoma, glioblastoma, urothelial carcinoma, urinary bladder cancer, uterus cancer (including uterine cervical cancer and uterine body cancer), primary central nervous system lymphoma, primary testicular lymphoma, biliary tract cancer, brain tumor, prostate cancer, leukemia, lymphoma, liver cancer, sarcoma, fibrosarcoma, mastocytoma, adrenocortical carcinoma, Ewing's tumor, multiple myeloma, testicular cancer, thyroid cancer, basal cell carcinoma, Paget's disease, or skin cancer. In addition, these cancers may be primary cancers, metastatic cancers, cancers that have metastasized, cancers that have recurred, postoperative cancers, or unresectable cancers. In this regard, melanoma is often used synonymously with malignant melanoma.

[0128]

Other examples of a cancer targeted in the present invention include a cancer resistant to a known treatment method. The cancer having resistance is not particularly limited and may be a cancer derived from a patient having any history of treatment. The cancer is, for example, a cancer derived from a patient having a history of treatment with 5-FU, which has come to have resistance, the cancer metastasized, or the cancer recurred after the administration.

[0129]

More specifically, examples of the cancer include, but are not limited to, for example, Bowen's disease, melanoma, prickle cell cancer, extramammary Paget's disease, mycosis fungoides, Sezary's syndrome, cutaneous T/NK-cell lymphoma, T-cell leukemia or lymphoma having a lesion only in the skin, cutaneous B-cell lymphoma (indolent group), cutaneous T-cell lymphatic or mammary adenoma, complex mammary adenoma, malignant mixed tumor of mammary gland, intraductal papillary carcinoma of mammary gland, lung adenocarcinoma, squamous cell cancer, small cell cancer, large cell cancer, glioma which is a neuroepithelial tissue tumor, glioblastoma, neuroblastoma, ependymoma, neuronal tumor, embryonal neuroectodermal tumor, neurilemoma, neurofibromatosis, meningioma, chronic lymphocytic leukemia, lymphoma, alimentary lymphoma, gastrointestinal lymphoma, small to medium cell lymphoma, cecal cancer, ascending colon cancer, descending colon cancer, transverse colon

cancer, sigmoid colon cancer, rectal cancer, ovarian epithelial cancer, germ cell tumor, interstitial cell tumor, pancreatic duct cancer, invasive pancreatic duct cancer, adenocarcinoma of pancreatic cancer, acinar cell cancer, adenosquamous cancer, giant cell tumor, intraductal papillary mucinous tumor, mucinous cystadenocarcinoma, pancreatoblastoma, pancreatic islet cell tumor, Frantz's tumor, serous cystadenocarcinoma, solid pseudopapillary cancer, gastrinoma, glucagonoma, insulinoma, multiple endocrine neoplasia type-1 (Wermer syndrome), nonfunctional islet cell tumor, somatostatinoma, VIPoma, uterine cervical cancer, uterine body cancer, fibrosarcoma, osteosarcoma, joint sarcoma, Ewing sarcoma, Wilms's tumor, hepatoblastoma, soft tissue sarcoma, acute leukemia, chronic leukemia, spinal cord tumor, malignant soft tissue tumor, tumors of teratoma group, and head and neck cancer including hypopharynx cancer, oropharynx cancer, tongue cancer, nasopharyngeal cancer, oral cavity cancer, lip cancer, sinus cancer, voice box cancer, ureteropelvic cancer, urinary bladder cancer, urethral cancer, testicular neoplasm, malignant pleural mesothelioma, malignant bone tumor, uterine body cancer (with a postoperative chemotherapy or a chemotherapy for metastasis and recurrence), pediatric malignant solid tumor (rhabdomyosarcoma, neuroblastoma, hepatoblastoma, medulloblastoma, nephroblastoma, retinoblastoma, central nervous system germ cell tumor, and Ewing sarcoma family of tumors), serous tumor (encompassing serous borderline malignant tumor (SBT)), mucinous tumor, surface epithelial borderline malignant tumor, interstitial borderline malignant tumor, and the like. The cancer also includes a palpable cancer, a subcutaneously existing cancer, an intracutaneously existing cancer, a superficial cancer, cancer existing in the dermis, cancer existing in a non-parenchymal organ, and a progressive cancer, which originate from the cancers described above. The cancer also includes a palpable cancer, a subcutaneously existing cancer, an intracutaneously existing cancer, a superficial cancer, cancer existing in the dermis and cancer existing in a non-parenchymal organ, which originate from the cancers described above and have metastasized and recurred.

[0130]

A preferable subject (patient) that can be a target is a mammal and is, for example, a mammal including primates, pet animals, livestock animals, and sport animals. Humans, dogs and cats are particularly preferable.

[0131]

A medicament of the present invention can be formulated by a method known to persons skilled in the art. For instance, a medicament according to the present invention can be parenterally used in the form of a parenteral injection of: an aseptic solution in water or a pharmacologically acceptable non-water solution; or a suspension liquid. For each formulation or pharmaceutical composition in a medicament according to the present invention, the active ingredients thereof (at least one of an anti-CAPRIN-1 antibody, a pyrimidine-based drug, a platinum formulation, or an angiogenesis inhibitor) may be combined, for example, with a pharmacologically acceptable carrier, a medium, or an additive, specifically sterilized water, physiological saline, an isotonic solution, a buffering agent (buffer solution or the like), plant oil, oily oil, an antioxidant, a dissolution aid, an emulsifier, a suspension, a surfactant, a stabilizer, a fragrance, an excipient, a binder, or the like in an appropriate manner, and preferably may be mixed with such a component in a unit dosage form required for a generally acceptable pharmaceutical formulation. An amount of an active ingredient in a formulation is determined such that an appropriate dosage within an indicated range can be achieved.

[0132]

An aseptic composition for injection can be prepared in accordance with general formulation practice using a vehicle such as distilled water for injection. An aqueous solution for injection purposes includes, for example, physiological saline or isotonic solutions comprising glucose and other adjuvants such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride. Such solution may be used with an appropriate dissolution aid. Such dissolution aid includes, for example, alcohols such as ethanol and polyalcohol, such as propylene glycol, polyethylene glycol, or nonion surfactants such as polysorbate 80(TM) and HCO-60. Oily liquid includes, for example, sesame oil or soybean oil. Such oily liquid may be used in combination with a dissolution aid such as benzyl benzoate or benzyl alcohol. In addition, it may be mixed with a buffering agent such as a phosphate buffer solution or a sodium acetate buffer solution, a soothing agent such as procaine hydrochloride, a stabilizer such as benzyl alcohol or phenol, or an antioxidant. In general, a formulated injection solution is introduced into an adequate ampule.

[0133]

The above pharmaceutical composition is orally or parenterally administered. Preferably, it is parenterally administered. Specifically, dosage forms include forms of injectable agents, intranasally-administered agents, transpulmonarily-administered agents, and percutaneously-administered agents. For example, with the form of injectable agents, administration may be systemically or locally via intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, or intratumoral injection. The form of percutaneously-administered agents include, for example, agents called liniments and external medicines. The external medicines include, for example, solid agents, solutions, sprays, ointments, creams, and gels.

[0134]

The administration method can be appropriately determined depending on age, weight, sex, and symptoms of a patient. The dose of a pharmaceutical composition comprising at least one of an anti-CAPRIN-1 antibody, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor can be selected within a range of, for example, 0.0001 mg to 1000 mg per kg of body weight per dose, as the amount of each active ingredient. Alternatively, the dose of each active ingredient can be selected within a range of, for example, 0.001 to 100000 mg per patient's body or 1 mg to 30 mg per kg of patient's body weight; however, it is not necessarily limited thereto. The dose and the administration method are changed depending on patient age, weight, gender, and symptoms. However, persons skilled in the art can appropriately select the dose and the method.

[0135]

<Administration method>

Treatment and/or prevention of cancer with a medicament for treatment and/or prevention of cancer of the present invention includes various modes, in addition to administration as a medicament mentioned above. For example, respective active ingredients in a medicament of the present invention can be administered simultaneously, in parallel, or individually in a staggered manner. As a specific example, the second, third, and fourth active ingredients can be administered within a time interval up to approximately 3 weeks after

administration of the first active ingredient, i.e., the active ingredients can be administered from immediately after up to approximately 3 weeks after administration of the first active ingredient. These administrations may be carried out subsequently to a surgical procedure, or a surgical procedure may be carried out between the administration of the first drug and the administrations of the second, third, and fourth drugs. In addition, the medicament for treatment and/or prevention of cancer of the present invention may be administered according to a plurality of administration cycles. For example, in the case of carrying out simultaneous administration of respective active ingredients in a medicament for treatment and/or prevention of cancer of the present invention, a pharmaceutical composition comprising the active ingredients (an anti-CAPRIN-1 antibody, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor) of the present invention is administered once per approximately 2 days to approximately 3 weeks as one cycle. Then, this treatment cycle may be repeated, if necessary, according to the judgment of a physician in charge. Likewise, in the case of scheduling a formulation in a staggered manner, respective administration periods of individual agents are adjusted so as to span the same period. The interval between cycles can vary from 0 to 2 months. Doses of the respective active ingredients in a medicament for treatment and/or prevention of cancer of the present invention can be set in the same way as in the doses of the respective active ingredients in the pharmaceutical composition.

[0136]

<Pharmaceutical kit>

A medicament for treatment and/or prevention of cancer of the present invention may be in the form of a pharmaceutical kit. The pharmaceutical kit may be a package for using active ingredients in the form of separate pharmaceutical compositions (formulations) in a method for treating and/or preventing cancer, and may comprise an instruction for administering each of the active ingredients. The respective active ingredients in the pharmaceutical compositions for treatment and/or prevention of cancer contained in the pharmaceutical kit can be in the form of pharmaceutical compositions each formulated as described above such that the active ingredients can be administered together or separately. Further, the pharmaceutical kit

comprises active ingredients in amounts sufficient for one or more doses such that the active ingredients can be administered according to the administration method described above.

[0137]

<Method for treatment and/or prevention>

On the basis of the contents specifically described above, the present invention provides a method for treating and/or preventing cancer, comprising administering, to a subject (patient), the medicament of the present invention or the anti-CAPRIN-1 antibody, and the pyrimidine-based drug, platinum formulation, and angiogenesis inhibitor of the present invention. For example, the present invention further provides a method for treating and/or preventing cancer, comprising administering the medicament or the like of the present invention as described above to a subject (patient) having cancer or suspected of having cancer. In the method of the present invention, another antitumor agent (a known antitumor agent or the like) in addition to the anti-CAPRIN-1 antibody, and the pyrimidine-based drug, platinum formulation, and angiogenesis inhibitor of the present invention may be administered to a subject (patient). In this embodiment, for example, an anti-CAPRIN-1 antibody or a fragment thereof, and a pyrimidine-based drug, a platinum formulation, an angiogenesis inhibitor, and optionally an antitumor agent contained in the medicament can be administered simultaneously or separately to the subject (patient).

Examples

[0138]

The present invention is hereafter described in detail with reference to the following examples, although the scope of the present invention is not limited thereto.

[0139]

(Example 1) Production of anti-CAPRIN-1 antibody

As anti-CAPRIN-1 antibodies having an immunological reactivity with CAPRIN-1 protein used in the present invention, antibodies were produced as described below for use.

[0140]

(Polyclonal antibody)

1mg of a human CAPRIN-1 recombinant protein (SEQ ID NO: 2) produced according to Example 3 of WO2010/016526 was mixed with an incomplete Freund's adjuvant (IFA) solution in an amount equivalent to the recombinant protein. The mixture was subcutaneously administered to a rabbit four times every 2 weeks. Subsequently, blood was collected, so that an antiserum containing a polyclonal antibody was obtained. Furthermore, the antiserum was purified using a protein G carrier (GE Healthcare Bio-Sciences) and replaced with PBS(-) and then a polyclonal antibody against CAPRIN-1 protein (anti-CAPRIN-1 polyclonal antibody #1) was obtained.

[0141]

(Monoclonal antibody)

100µg of a human CAPRIN-1 recombinant protein produced according to Example 3 of WO2010/016526 was mixed with an MPL+TDM adjuvant (Sigma) in an amount equivalent to that of the antigen protein. The mixture was used as an antigen solution per mouse. The antigen solution was administered intraperitoneally to 6-week-old Balb/c mice (Japan SLC Inc.) and then further administered 3 times and 24 times every week for completion of immunization. A spleen was removed on day 3 from the final immunization and then ground between two sterilized glass slides. Spleen cells were obtained by repeating the following procedure three times: washing with PBS(-) (manufactured by Nissui Pharmaceutical Co., Ltd.), centrifuging at 1500 rpm for 10 minutes, and removing the supernatant. The obtained spleen cells were mixed with mouse myeloma cell SP2/0 (purchased from ATCC) at a ratio of 10:1. The PEG solution prepared by mixing 200 µl of RPMI1640 medium containing 10% FBS heated at 37°C and 800 µl of PEG1500 (Boehringer) was added to the cells. The solution was incubated for 5 minutes for cell fusion. Centrifugation was performed at 1700 rpm for 5 minutes, and the supernatants were removed. Cells were suspended in 150 ml of RPMI1640 medium (HAT selective medium) containing 15% FBS, to which 2% equivalent of HAT solution (Gibco) had been added and then seeded onto fifteen 96-well plates (Nunc) at 100 µl per well. Cells were cultured for 7 days under conditions of 37°C and 5% CO₂, so that hybridomas resulting from fusion of spleen cells to myeloma cells were obtained. Hybridomas were selected using binding affinity to CAPRIN-1 protein of the antibody produced by the prepared hybridomas as an indicator. The

CAPRIN-1 protein solution (1 µg/ml) was added at 100 µl per well of 96-well plates and then incubated at 4°C for 18 hours. After each well was washed three times with PBS-T, 0.5% Bovine Serum Albumin (BSA) solution (Sigma) was added at 400 µl per well, and then the plates were incubated at room temperature for 3 hours. The solution was removed and then each well was washed three times with 400 µl of PBS-T. Each culture supernatant of the hybridomas obtained above was added at 100 µl per well and then incubated at room temperature for 2 hours. After each well was washed three times with PBS-T, an HRP-labeled anti-mouse IgG (H+L) antibody (Invitrogen) diluted 5000-fold with PBS was added at 100 µl per well and then incubated at room temperature for 1 hour. After each well was washed three times with PBS-T, a TMB substrate solution (Thermo) was added at 100 µl per well and then incubated for 15-30 minutes, so that a color reaction was performed. After color development, 1 N sulfuric acid was added at 100 µl per well to stop the reaction. Absorbance at 450 nm and absorbance at 595 nm were measured using an absorption spectrometer. As a result, a plurality of hybridomas producing antibodies with high absorbances were selected. The selected hybridomas were added at 0.5 hybridomas per well of 96-well plates and then cultured. After 1 week, hybridomas forming single colonies in wells were observed. Cells in these wells were further cultured. Hybridomas were selected using binding affinity to CAPRIN-1 protein of the antibody produced by cloned hybridomas as an indicator. The CAPRIN-1 protein solution (1 µg/ml) was added at 100 µl per well of 96-well plates and then incubated at 4°C for 18 hours. Each well was washed three times with PBS-T, and a 0.5% BSA solution was added at 400 µl per well, and then incubated at room temperature for 3 hours. The solution was removed and then each well was washed three times with 400 µl of PBS-T. Each culture supernatant of the hybridomas obtained above was added at 100 µl per well and then incubated at room temperature for 2 hours. Each well was washed three times with PBS-T, an HRP-labeled anti-mouse IgG (H+L) antibody (Invitrogen) diluted 5000-fold with PBS was added at 100 µl per well and then incubated at room temperature for 1 hour. Each well was washed three times with PBS-T, a TMB substrate solution (Thermo) was added at 100 µl per well and then incubated for 15-30 minutes, so that a color reaction was performed. After color development, 1 N sulfuric acid was added at 100 µl per well to stop the reaction. Absorbance at 450 nm and absorbance at

595 nm were measured using an absorption spectrometer. As a result, a plurality of mouse monoclonal antibodies exerting reactivity with CAPRIN-1 protein were obtained.

[0142]

Reactivity of each monoclonal antibody with human cancer cells confirmed to express CAPRIN-1 protein on cell membrane surfaces was further confirmed by flow cytometry. A mouse IgG control antibody exhibiting no reactivity with the cancer cells was used as a negative control. As a result of confirmation, several monoclonal antibodies were obtained which had stronger fluorescence intensity against the cancer cells than that of the mouse IgG control antibody and reacted strongly with the cell membrane surfaces of the cancer cells expressing CAPRIN-1 on the cell membrane surfaces. Among them, a monoclonal antibody against CAPRIN-1 described in WO2013/125630, which was an antibody in the above-mentioned (ab) comprising the amino acid sequence of a heavy-chain variable region shown by SEQ ID NO: 114 and the amino acid sequence of a light-chain variable region shown by SEQ ID NO: 115, was selected as a monoclonal antibody exhibiting reactivity with CAPRIN-1 protein.

[0143]

CDR1 to CDR3 of the heavy-chain variable region of the antibody selected were identified. A nucleotide sequence was designed so as to be able to express a heavy-chain variable region in which framework regions comprise a human antibody sequence. This nucleotide sequence was inserted to a vector for mammalian expression having an insert of a human IgG1 heavy-chain constant region. Likewise, CDR1 to CDR3 of the light-chain variable region were identified. A nucleotide sequence was designed so as to be able to express a light-chain variable region in which framework regions comprise a human antibody sequence. This nucleotide sequence was inserted to a vector for mammalian expression having an insert of a human IgG1 light-chain constant region. These two recombinant expression vectors were introduced to mammalian cells according to a general method and then a culture supernatant containing humanized monoclonal antibody #1 (humanized antibody #1) against CAPRIN-1.

[0144]

The obtained culture supernatant containing the obtained humanized anti-CAPRIN-1 monoclonal antibody #1 was purified using Hitrap Protein A Sepharose FF (GE Healthcare Bio-

Sciences) according to a general method, replaced with PBS(-), and filtered through a 0.22 μ m filter (Millipore) for preparation of the filtrate.

[0145]

The specific reactivity of the anti-CAPRIN-1 antibody to CAPRIN-1 protein was detected and confirmed by ELISA using CAPRIN-1 protein immobilized on a plate.

[0146]

The reactivity of the anti-CAPRIN-1 antibody with cancer cells without permeation treatment of cell membranes was examined by flow cytometry to confirm that a portion of CAPRIN-1 was expressed on cell membrane surfaces of cancer cells as shown by Examples given below.

[0147]

It was confirmed by flow cytometry that, against all of breast cancer cells (BT-474), colon cancer cells (HT-29), lung cancer cells (QG56 and H1650), gastric cancer cells (NCI-N87), uterus cancer cells (HEC-1-A), prostate cancer cells (22Rv1), pancreatic cancer cells (Panc10.5), liver cancer cells (Hep3B), ovarian cancer cells (SKOV3), kidney cancer cells (Caki-2), brain tumor cells (U-87MG), urinary bladder cancer cells (T24), esophageal cancer cells (OE33), leukemia cells (OCI-AML5), lymphoma cells (Ramos), gallbladder cancer cells (TGBC14TKB), fibrosarcoma cells (HT-1080), and melanoma cells (G-361), which are human cancer cells confirmed to express CAPRIN-1 gene; and mouse kidney cancer cells (Renca) and mouse breast cancer cells (4T1) confirmed to express CAPRIN-1 gene, the humanized antibody #1 had stronger fluorescence intensity than that of a human IgG control antibody and rabbit IgG antibody serving as negative controls exhibiting no reactivity with the cancer cells, and reacted strongly with the cell membrane surfaces of the cancer cells expressing CAPRIN-1.

[0148]

Similarly, it was confirmed that each of those anti-CAPRIN-1 antibodies described in (a) to (aa) and (ac) to (al) above which are described in WO2010/016526, WO2011/096517, WO2011/096528, WO2011/096519, WO2011/096533, WO2011/096534, WO2011/096535, WO2013/018886, WO2013/018894, WO2013/018892, WO2013/018891, WO2013/018889, WO2013/018883, WO2013/125636, WO2013/125654, WO2013/125640, WO2013/147169,

WO2013/147176, and WO2015/020212 also reacted strongly with the cell membrane surface of the cancer in the same manner.

[0149]

(Example 2) Antitumor effect of a combined use of anti-CAPRIN-1 antibody and gemcitabine/carboplatin/bevacizumab therapy in mouse model bearing cancer of human cancer cell

An *in vivo* antitumor effect in a cancer-bearing mouse by a combined use of the anti-CAPRIN-1 antibody (anti-CAPRIN-1 humanized antibody #1) produced in Example 1 and a gemcitabine/carboplatin/bevacizumab therapy was evaluated.

[0150]

Specifically, the antitumor effect of the combined use of an anti-CAPRIN-1 antibody and gemcitabine/carboplatin/bevacizumab according to the present invention was studied using NOD-SCID mice in which human-derived cancer cells expressing CAPRIN-1 protein were subcutaneously transplanted. Human breast cancer cells BT474 were subcutaneously transplanted at 2×10^7 cells per mouse as a mixture with Matrigel (Sigma) and allowed to grow until a tumor became approximately 164 to 165 mm³ to prepare cancer-bearing mice. The BT474 is a cancer cell which expresses CAPRIN-1 protein on cell membrane surfaces, and for which the anti-CAPRIN-1 antibodies produced in Example 1 were confirmed to react with a portion of CAPRIN-1 present on the cell membrane surfaces. Each anti-CAPRIN-1 antibody produced in Example 1 was administered at 10 mg/kg once a week, four times in total, via the tail veins of eight cancer-bearing mice described above. To each of the same mice, gemcitabine, carboplatin, and bevacizumab were administered at 5 mg/kg, 15 mg/kg, and 1.25 mg/kg respectively at the same time as an anti-CAPRIN-1 antibody was administered. Gemcitabine was administered twice a week, eight times in total, and carboplatin and bevacizumab were administered once a week, four times in total.

[0151]

For a comparative control group, the same dose of the same anti-CAPRIN-1 antibody as above was administered once a week to cancer-bearing mice. For another comparative control group, only gemcitabine/carboplatin, only gemcitabine/carboplatin/bevacizumab, or

gemcitabine/carboplatin simultaneously with an anti-CAPRIN-1 antibody were administered to other cancer-bearing mouse individuals at the same administration intervals. Cancer-bearing mice in a non-treatment group were used as negative controls. After the start of administration, the sizes of cancers in the cancer-bearing mice were measured over time using calipers. The tumor volume of each individual was calculated according to a standard method using a calculation formula: (Length of the major axis of the tumor) $\times$ (Length of the minor axis of the tumor)² $\times$ 0.5, and the average of the treated group was calculated.

[0152]

As the result of the evaluation, the tumor volumes of the comparative control groups were as follows: the tumor volume of the treated group to which the anti-CAPRIN-1 humanized antibody #1 produced in Example 1 was administered was 34%, the tumor volume of the gemcitabine/carboplatin treated group was 43%, and the tumor volume of the gemcitabine/carboplatin/bevacizumab treated group was 26%, in approximately one week after the termination of administration of the drug (on day 48 after bearing cancer), assuming that the tumor volume of the negative control was 100%. Thus, the tumor volume was increased compared to at the start of the administration. In addition, the tumor volume of the group to which a combination of the three agents, namely, the humanized antibody #1 produced in Example 1 and gemcitabine/carboplatin was administered was 17%. Thus, the tumor volume was not found to be increased, and still was not reduced. On the other hand, the tumor volume of the group to which a combination of the four agents, namely, the humanized antibody #1 produced in Example 1 and gemcitabine/carboplatin/bevacizumab was administered was 5%. The tumor volume was reduced compared to at the start of the administration.

[0153]

The follow-up of the tumor volume was continued after the termination of administration of a drug, and the tumor volumes of the comparative control groups were as follows: the tumor volume of the treated group to which the anti-CAPRIN-1 humanized antibody #1 produced in Example 1 was administered was 1616 mm³, the tumor volume of the gemcitabine/carboplatin treated group was 1736 mm³, and tumor volume of the gemcitabine/carboplatin/bevacizumab treated group was 1757 mm³, in approximately seven weeks after the termination of

administration of a drug (on day 87 after bearing cancer). Thus, no difference was observed between the gemcitabine/carboplatin treated group and the gemcitabine/carboplatin/bevacizumab treated group. On the other hand, the group treated with a combination of three agents, namely, the humanized antibody #1 produced in Example 1 and gemcitabine/carboplatin and the group treated with a combination of four agents, namely, the humanized antibody #1 produced in Example 1 and gemcitabine/carboplatin/bevacizumab gave 860 mm³ and 288 mm³ respectively. Thus, the group treated with a combination of the four agents exhibited a remarkable antitumor effect.

[0154]

Furthermore, in the same evaluation system as described above, the antitumor effects in the cancer-bearing mice by a combined use of the anti-CAPRIN-1 antibody (anti-CAPRIN-1 humanized antibody #1) produced in Example 1 and a gemcitabine/carboplatin/bevacizumab therapy and a combined use of the anti-CAPRIN-1 antibody (anti-CAPRIN-1 humanized antibody #1) and a bevacizumab therapy were evaluated, with the result that the tumor was not found to be reduced in the group to which the humanized antibody #1 and bevacizumab were administered in combination, but that the tumor was found to be decreased with the humanized antibody #1 and the gemcitabine/carboplatin/bevacizumab therapy.

[0155]

Similarly, it was shown that each of the anti-CAPRIN-1 antibodies described in (a) to (aa) and (ac) to (al) above which are described in WO2010/016526, WO2011/096517, WO2011/096528, WO2011/096519, WO2011/096533, WO2011/096534, WO2011/096535, WO2013/018886, WO2013/018894, WO2013/018892, WO2013/018891, WO2013/018889, WO2013/018883, WO2013/125636, WO2013/125654, WO2013/125640, WO2013/147169, WO2013/147176, and WO2015/020212 had a remarkably stronger antitumor effect when administered in combination with gemcitabine/carboplatin/bevacizumab than in a case where the anti-CAPRIN-1 antibody alone was administered, in a case where gemcitabine/carboplatin were administered, in a case where gemcitabine/carboplatin/bevacizumab were administered, in a case where the anti-CAPRIN-1 antibody and bevacizumab were administered, and in a case where the anti-CAPRIN-1 antibody and gemcitabine/carboplatin were administered.

[0156]

The results of this evaluation have demonstrated that each of the anti-CAPRIN-1 antibodies had a remarkably stronger antitumor effect when administered in combination with gemcitabine/carboplatin/bevacizumab than in a case where the anti-CAPRIN-1 antibody alone was administered, in a case where gemcitabine/carboplatin were administered, in a case where gemcitabine/carboplatin/bevacizumab were administered, in a case where the anti-CAPRIN-1 antibody and bevacizumab were administered, and in a case where the anti-CAPRIN-1 antibody and gemcitabine/carboplatin were administered.

CLAIMS

[Claim 1]

A medicament for treatment and/or prevention of cancer, comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor, together or separately in combination, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor, together or separately in combination.

[Claim 2]

The medicament according to claim 1, wherein the cancer is a cancer in a cancer patient having a medical history of a cancer treatment with a pyrimidine-based drug and/or a platinum formulation.

[Claim 3]

The medicament according to claim 1 or 2, wherein the cancer is a cancer in a cancer patient for whom a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; carboplatin; and an angiogenesis inhibitor, together or separately in combination, was not effective.

[Claim 4]

The medicament according to any one of claims 1 to 3, wherein the cancer is a cancer in a cancer patient for whom a cancer treatment with a pyrimidine-based drug and/or a platinum formulation was not effective.

[Claim 5]

The medicament according to any one of claims 1 to 4, wherein the pyrimidine-based drug is gemcitabine and/or a derivative of gemcitabine.

[Claim 6]

The medicament according to any one of claims 1 to 5, wherein the angiogenesis inhibitor is bevacizumab.

[Claim 7]

The medicament according to any one of claims 1 to 6, wherein the platinum formulation is carboplatin, cisplatin, oxaliplatin, nedaplatin, and/or miriplatin.

[Claim 8]

The medicament according to any one of claims 1 to 7, wherein the antibody or the fragment thereof has an immunological reactivity with CAPRIN-1 protein having an amino acid sequence shown by any one of the even numbered SEQ ID NOs among SEQ ID NOs: 2 to 30, or an amino acid sequence having 80% or more sequence identity with the amino acid sequence.

[Claim 9]

The medicament according to any one of claims 1 to 8, wherein the antibody or the fragment thereof has an immunological reactivity with an extracellular region of CAPRIN-1 protein present on a cancer cell surface.

[Claim 10]

The medicament according to any one of claims 1 to 9, wherein the antibody or the fragment thereof has an immunological reactivity with a partial polypeptide of CAPRIN-1 protein, the partial polypeptide having an amino acid sequence represented by any one of SEQ ID NOs: 31 to 35, 296 to 299, 308 and 309, or an amino acid sequence having 80% or more sequence identity with the amino acid sequence.

[Claim 11]

The medicament according to any one of claims 1 to 10, wherein the antibody is a monoclonal antibody or a polyclonal antibody.

[Claim 12]

The medicament according to any one of claims 1 to 11, wherein the antibody or the fragment thereof is any one of the following (A) to (M):

(A) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 36, 37 and 38 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions

of SEQ ID NOs: 40, 41 and 42 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(B) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 44, 45 and 46 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 48, 49 and 50 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(C) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 52, 53 and 54 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 56, 57 and 58 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(D) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 60, 61 and 62 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 64, 65 and 66 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(E) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 170, 171 and 172 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 173, 174 and 175 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(F) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 176, 177 and 178 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 179, 180 and 181 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(G) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 182, 183 and 184 (CDR1, CDR2 and

CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 185, 186 and 187 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(H) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 188, 189 and 190 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 191, 192 and 193 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(I) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 146, 147 and 148 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 149, 150 and 151 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(J) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 272, 273 and 274 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 275, 276 and 277 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(K) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 290, 291 and 292 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 293, 294 and 295 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein;

(L) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 301, 302 and 303 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 305, 306 and 307 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein; and

(M) an antibody or a fragment thereof comprising a heavy-chain variable region comprising complementarity determining regions of SEQ ID NOs: 134, 135 and 136 (CDR1, CDR2 and CDR3, respectively) and a light-chain variable region comprising complementarity determining regions of SEQ ID NOs: 137, 138 and 139 (CDR1, CDR2 and CDR3, respectively), and having an immunological reactivity with CAPRIN-1 protein.

[Claim 13]

The medicament according to any one of claims 1 to 11, wherein the antibody or the fragment thereof is any one of the following (a) to (al):

- (a) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 39 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 43;
- (b) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 47 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 51;
- (c) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 55 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 59;
- (d) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 63 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 67;
- (e) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 68 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 69;
- (f) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 70 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 71;
- (g) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 72 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 73;

- (h) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 74 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 75;
- (i) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 76 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 77;
- (j) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 78 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 79;
- (k) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 80 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 81;
- (l) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 82 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 83;
- (m) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 84 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 85;
- (n) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 86 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 87;
- (o) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 88 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 89;
- (p) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 90 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 91;

- (q) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 92 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 93;
- (r) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 94 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 95;
- (s) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 96 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 97;
- (t) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 98 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 99;
- (u) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 100 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 101;
- (v) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 102 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 103;
- (w) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 104 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 105;
- (x) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 106 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 107;
- (y) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 108 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 109;

- (z) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 110 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 111;
- (aa) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 112 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 113;
- (ab) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 114 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 115;
- (ac) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 116 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 117;
- (ad) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 118 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 119;
- (ae) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 120 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 121;
- (af) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 122 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 123;
- (ag) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 124 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 125;
- (ah) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 126 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 127;

(ai) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 128 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 129;

(aj) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 130 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 131;

(ak) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 132 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 133; and

(al) an antibody or a fragment thereof comprising a heavy-chain variable region comprising the amino acid sequence of SEQ ID NO: 300 and a light-chain variable region comprising the amino acid sequence of SEQ ID NO: 304.

[Claim 14]

The medicament according to any one of claims 1 to 13, wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody or a single chain antibody.

[Claim 15]

The medicament according to any one of claims 1 to 14, wherein the cancer is a cancer expressing CAPRIN-1 protein on a cell membrane surface.

[Claim 16]

The medicament according to any one of claims 1 to 15, wherein the cancer is ovarian cancer, bile duct cancer, breast cancer, kidney cancer, pancreatic cancer, colon cancer, melanoma, lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, gastric cancer, mesothelial cancer, colorectal cancer, esophageal cancer, gastroesophageal junction cancer, hepatocellular carcinoma, glioblastoma, urothelial carcinoma, urinary bladder cancer, uterus cancer, primary central nervous system lymphoma, primary testicular lymphoma, biliary tract cancer, brain tumor, prostate cancer, leukemia, lymphoma, liver cancer, sarcoma, fibrosarcoma, mastocytoma, adrenocortical carcinoma, Ewing's tumor, multiple myeloma, testicular cancer, thyroid cancer, basal cell carcinoma, Paget's disease, or skin cancer.

[Claim 17]

An agent increasing drug efficacy of a pharmaceutical composition for treatment and/or prevention of cancer, wherein the agent comprises, as active ingredients, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, wherein the pharmaceutical composition comprises, as an active ingredient, an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with a medicament comprising: the antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; the pyrimidine-based drug; the platinum formulation; and the angiogenesis inhibitor, together or separately in combination.

[Claim 18]

A drug efficacy increasing agent of a pharmaceutical composition for treatment and/or prevention of cancer, wherein the agent comprises, as an active ingredient, an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein, wherein the pharmaceutical composition comprises, as active ingredients, a pyrimidine-based drug, a platinum formulation, and an angiogenesis inhibitor, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with a medicament comprising: the antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; the pyrimidine-based drug; the platinum formulation; and the angiogenesis inhibitor, together or separately in combination.

[Claim 19]

A method for treating and/or preventing cancer, comprising administering: an antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; a pyrimidine-based drug; a platinum formulation; and an angiogenesis inhibitor, together or separately to a subject, wherein a cancer patient with the cancer is a cancer patient having a medical history of a cancer treatment with a medicament other than a cancer treatment with the medicament comprising: the antibody or a fragment thereof having an immunological reactivity with CAPRIN-1 protein; the pyrimidine-based drug; the platinum formulation; and the angiogenesis inhibitor, together or separately in combination.

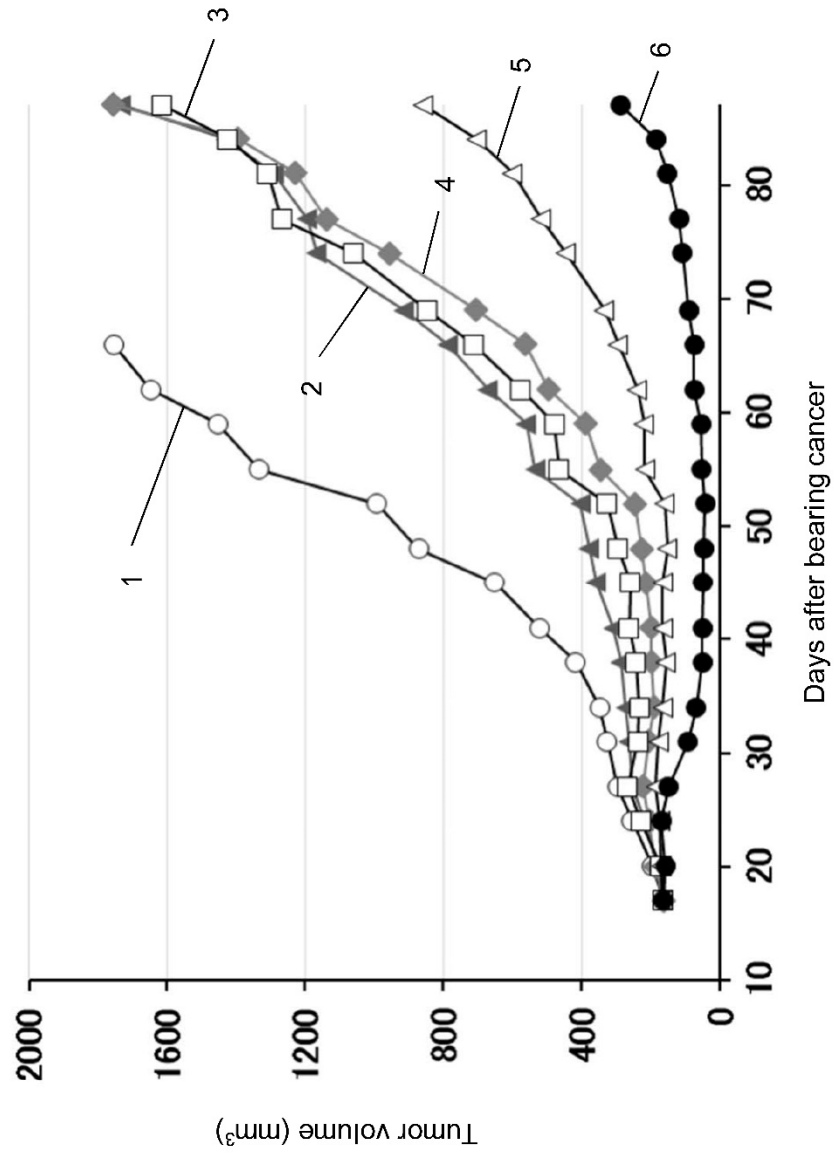


Fig. 1

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 ttg gga gat gat gaa gtg cgg act gac ctg aaa caa ggt ttg aat gga 711
 Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly
 160 165 170
 gtg cca ata ttg tcc gaa gag gag ttg tca ttg ttg gat gaa ttc tat 759
 Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr
 175 180 185 190

aag cta gta gac cct gaa cgg gac atg agc ttg agg ttg aat gaa cag	807
Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln	
195 200 205	
tat gaa cat gcc tcc att cac ctg tgg gac ctg ctg gaa ggg aag gaa	855
Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu	
210 215 220	
aaa cct gta tgt gga acc acc tat aaa gtt cta aag gaa att gtt gag	903
Lys Pro Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu	
225 230 235	
cgt gtt ttt cag tca aac tac ttt gac agc acc cac aac cac cag aat	951
Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn	
240 245 250	
ggg ctg tgt gag gaa gaa gag gca gcc tca gca cct gca gtt gaa gac	999
Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp	
255 260 265 270	
cag gta cct gaa gct gaa cct gag cca gca gaa gag tac act gag caa	1047
Gln Val Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln	
275 280 285	
agt gaa gtt gaa tca aca gag tat gta aat aga cag ttc atg gca gaa	1095
Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu	
290 295 300	
aca cag ttc acc agt ggt gaa aag gag cag gta gat gag tgg aca gtt	1143
Thr Gln Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val	
305 310 315	
gaa acg gtt gag gtg gta aat tca ctc cag cag caa cct cag gct gca	1191
Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala	
320 325 330	
tcc cct tca gta cca gag ccc cac tct ttg act cca gtg gct cag gca	1239
Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala	
335 340 345 350	
gat ccc ctt gtg aga aga cag cga gta caa gac ctt atg gca caa atg	1287
Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met	
355 360 365	
cag ggt ccc tat aat ttc ata cag gat tca atg ctg gat ttt gaa aat	1335
Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn	
370 375 380	
cag aca ctt gat cct gcc att gta tct gca cag cct atg aat cca aca	1383
Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr	
385 390 395	
caa aac atg gac atg ccc cag ctg gtt tgc cct cca gtt cat tct gaa	1431
Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu	
400 405 410	

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

Tyr	Arg	Pro	Ser	Phe	Ser	Asn	Thr	Pro	Asn	Ser	Gly	Tyr	Thr	Gln	Ser	
640						645					650					
cag	ttc	agt	gct	ccc	cgg	gat	tac	tct	ggc	tat	caa	cgg	gat	gga	tat	2199
Gln	Phe	Ser	Ala	Pro	Arg	Asp	Tyr	Ser	Gly	Tyr	Gln	Arg	Asp	Gly	Tyr	
655					660					665					670	
cag	cag	aat	ttc	aag	cga	ggc	tct	ggg	cag	agt	gga	cca	cgg	gga	gcc	2247
Gln	Gln	Asn	Phe	Lys	Arg	Gly	Ser	Gly	Gln	Ser	Gly	Pro	Arg	Gly	Ala	
				675					680					685		
cca	cga	ggt	aat	att	ttg	tgg	tgg	tga	tcctagctcc	taagtggagc						2294
Pro	Arg	Gly	Asn	Ile	Leu	Trp	Trp									
				690												
ttctgttctg	gccttgaag	agctgttaat	agctctgcatg	ttaggaatac	atttatcctt											2354
tccagacttg	ttgctaggga	ttaaataaaa	tgctctgttt	ctaaaactta	atcttggacc											2414
caaattttta	tttttgaatg	atttaatttt	ccctgttact	atataaactg	tcttgaaaac											2474
tagaacatat	tctcttctca	gaaaaagtgt	ttttccaact	gaaaattatt	tttcaggtcc											2534
taaaacctgc	taaatgtttt	taggaagtac	ttactgaaac	atTTTTgtaa	gacatttttg											2594
gaatgagatt	gaacatttat	ataaatttat	tattcctctt	tcattttttt	gaaacatgcc											2654
tattatattt	tagggccaga	caccctttta	tggccggata	agccatagtt	aacattttaga											2714
gaaccattta	gaagtgatag	aactaatgga	atttgcaatg	ccttttggac	ctctattagt											2774
gatataaata	tcaagttatt	tctgactttt	aaacaaaact	cccaaattcc	taacttattg											2834
agctataactt	aaaaaaaaatt	acaggtttag	agagtttttt	gtttttcttt	tactgttggg											2894
aaactacttc	ccattttggc	aggaagttaa	cctattttaac	aattagagct	agcatttcat											2954
gtagtctgaa	attctaaatg	gttctctgat	ttgaggagg	ttaaacaatca	aacaggtttc											3014
ctctattggc	cataacatgt	ataaaatgtg	tgtaaaggag	gaattacaac	gtactttgat											3074
ttgaatacta	gtagaaactg	gccaggaaaa	aggtacattt	ttctaaaaat	taatggatca											3134
cttggaatt	actgacttga	ctagaagtat	caaaggatgt	ttgcatgtga	atgtgggtta											3194
tgttctttcc	cacctttag	catattcgat	gaaagttgag	ttaactgata	gctaaaaatc											3254
tgttttaaca	gcatgtaaaa	agttatttta	tctgttaaaa	gtcattatac	agttttgaat											3314
gttatgtagt	ttctttttta	cagtttaggt	aataaggtct	gttttcattc	tggtgctttt											3374
attaattttg	atagtatgat	gttacttact	actgaaatgt	aagctagagt	gtacactaga											3434
atgtaagctc	catgagagca	ggtaccttgt	ctgtcttctc	tgctgtatct	attcccaacg											3494
cttgatgatg	gtgcctggca	catagtaggc	actcaataaa	tatttgttga	atgaatgaa											3553

<210> 4
 <211> 694
 <212> PRT
 <213> Homo sapiens

<400> 4

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

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

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

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

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

Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val
 85 90 95

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

Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys
 115 120 125

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

Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly
 145 150 155 160

Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro
 165 170 175

Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu
 180 185 190

Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu

195

200

205

His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro
 210 215 220

Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu Arg Val
 225 230 235 240

Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu
 245 250 255

Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln Val
 260 265 270

Pro Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu
 275 280 285

Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln
 290 295 300

Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr
 305 310 315 320

Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro
 325 330 335

Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro
 340 345 350

Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly
 355 360 365

Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr
 370 375 380

Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn
 385 390 395 400

Met Asp Met Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg
 405 410 415

Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val
 420 425 430

Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu
435 440 445

Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Ile
450 455 460

Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala
465 470 475 480

Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly
485 490 495

Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro
500 505 510

Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro
515 520 525

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

Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu
545 550 555 560

Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser
565 570 575

Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln
580 585 590

Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg
595 600 605

Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly
610 615 620

Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg
625 630 635 640

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

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

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

Gly Asn Ile Leu Trp Trp
690

<210> 5
<211> 1605
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (46).. (1392)

<400> 5
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Met Ala Leu Ser
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caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt 105
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
5 10 15 20

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc 153
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
25 30 35

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg 201
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
40 45 50

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tgc 249
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
55 60 65

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc 297
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
70 75 80

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac 345
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
85 90 95 100

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca 393
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
105 110 115

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc 441

Leu	Lys	Glu	Ile	Val	Glu	Arg	Val	Phe	Gln	Ser	Asn	Tyr	Phe	Asp	Ser	
			120					125					130			
act	cac	aac	cac	cag	aat	ggg	cta	tgt	gag	gaa	gaa	gag	gca	gcc	tca	489
Thr	His	Asn	His	Gln	Asn	Gly	Leu	Cys	Glu	Glu	Glu	Glu	Ala	Ala	Ser	
		135					140					145				
gca	cct	aca	gtt	gaa	gac	cag	gta	gct	gaa	gct	gag	cct	gag	cca	gca	537
Ala	Pro	Thr	Val	Glu	Asp	Gln	Val	Ala	Glu	Ala	Glu	Pro	Glu	Pro	Ala	
	150					155					160					
gaa	gaa	tac	act	gaa	caa	agt	gaa	gtt	gaa	tca	aca	gag	tat	gta	aat	585
Glu	Glu	Tyr	Thr	Glu	Gln	Ser	Glu	Val	Glu	Ser	Thr	Glu	Tyr	Val	Asn	
165					170					175					180	
aga	caa	ttt	atg	gca	gaa	aca	cag	ttc	agc	agt	ggc	gaa	aag	gag	cag	633
Arg	Gln	Phe	Met	Ala	Glu	Thr	Gln	Phe	Ser	Ser	Gly	Glu	Lys	Glu	Gln	
				185					190					195		
gta	gat	gag	tgg	acg	gtc	gaa	aca	gtg	gag	gtg	gtg	aat	tca	ctc	cag	681
Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	Gln	
			200					205					210			
cag	caa	cct	cag	gct	gcg	tct	cct	tca	gta	cca	gag	ccc	cac	tct	ttg	729
Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	Leu	
		215					220					225				
act	ccg	gtg	gct	cag	gca	gat	ccc	ctt	gtg	aga	aga	cag	cga	gtc	cag	777
Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln	
	230					235				240						
gac	ctt	atg	gcg	cag	atg	cag	ggg	ccc	tat	aat	ttc	ata	cag	gat	tca	825
Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Tyr	Asn	Phe	Ile	Gln	Asp	Ser	
245					250					255					260	
atg	ctg	gat	ttt	gaa	aac	cag	aca	ctc	gat	cct	gcc	att	gta	tct	gca	873
Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	Pro	Ala	Ile	Val	Ser	Ala	
				265					270					275		
cag	cct	atg	aat	ccg	aca	caa	aac	atg	gac	atg	ccc	cag	ctg	gtt	tgc	921
Gln	Pro	Met	Asn	Pro	Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	Cys	
			280					285					290			
cct	cca	gtt	cat	tct	gaa	tct	aga	ctt	gct	caa	cct	aat	caa	gtt	cct	969
Pro	Pro	Val	His	Ser	Glu	Ser	Arg	Leu	Ala	Gln	Pro	Asn	Gln	Val	Pro	
		295					300					305				
gta	caa	cca	gaa	gct	aca	cag	gtt	cct	ttg	gtt	tca	tcc	aca	agt	gag	1017
Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	Glu	
	310					315					320					
ggg	tat	aca	gca	tct	caa	ccc	ttg	tac	cag	cct	tct	cat	gct	aca	gag	1065
Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	Thr	Glu	
325					330					335					340	
caa	cga	cca	caa	aag	gaa	cca	att	gac	cag	att	cag	gca	aca	atc	tct	1113
Gln	Arg	Pro	Gln	Lys	Glu	Pro	Ile	Asp	Gln	Ile	Gln	Ala	Thr	Ile	Ser	

345	350	355	
tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser 360 365 370			1161
cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser 375 380 385			1209
gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe 390 395 400			1257
aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys 405 410 415 420			1305
caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln 425 430 435			1353
cct cac caa gta gaa caa aca gag gga tgc cgc aaa tga acactcagca Pro His Gln Val Glu Gln Thr Glu Gly Cys Arg Lys 440 445			1402
agtgaattaa tctgattcac aggattatgt ttaaacgccca aaaacacact ggccagtgtg			1462
ccataatatg ttaccagaag agttattatc tatttgttct ccctttcagg aaacttattg			1522
taaagggact gttttcatcc cataaagaca ggactacaat tgtcagcttt atattacctg			1582
gaaaaaaaaa aaaaaaaaaa aaa			1605

<210> 6
 <211> 448
 <212> PRT
 <213> Canis familiaris

<400> 6

Met	Ala	Leu	Ser	Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	Lys	Thr	Ala	Arg
1				5					10					15	

Arg	Glu	Gln	Leu	Met	Arg	Glu	Glu	Ala	Glu	Gln	Lys	Arg	Leu	Lys	Thr
			20					25					30		

Val	Leu	Glu	Leu	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	Asp	Asp	Glu	Val
		35					40					45			

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

Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu
65 70 75 80

Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile
85 90 95

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

Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn
115 120 125

Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu
130 135 140

Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu
145 150 155 160

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

Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly
180 185 190

Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val
195 200 205

Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu
210 215 220

Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg
225 230 235 240

Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe
245 250 255

Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala
260 265 270

Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro
275 280 285

Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro
 290 295 300

Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser
 305 310 315 320

Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser
 325 330 335

His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln
 340 345 350

Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu
 355 360 365

Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro
 370 375 380

Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met
 385 390 395 400

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

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

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

<210> 7
 <211> 4154
 <212> DNA
 <213> Canis familiaris

<220>
 <221> CDS
 <222> (1).. (2154)

<400> 7
 atg ccg tcg gcc acc agc ctc agc gga agc ggc agc aag tcg tcg ggc 48
 Met Pro Ser Ala Thr Ser Leu Ser Gly Ser Gly Ser Lys Ser Ser Gly
 1 5 10 15

ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg 96
 Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
 20 25 30 35 40 45 50

20	25	30	
ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln 35 40 45			144
cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln 50 55 60			192
atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys 65 70 75 80			240
ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu 85 90 95			288
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cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu 165 170 175			528
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ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser 195 200 205			624
ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp 210 215 220			672
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cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser 245 250 255			768

act	cac	aac	cac	cag	aat	ggg	cta	tgt	gag	gaa	gaa	gag	gca	gcc	tca	816
Thr	His	Asn	His	Gln	Asn	Gly	Leu	Cys	Glu	Glu	Glu	Glu	Ala	Ala	Ser	
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gca	cct	aca	gtt	gaa	gac	cag	gta	gct	gaa	gct	gag	cct	gag	cca	gca	864
Ala	Pro	Thr	Val	Glu	Asp	Gln	Val	Ala	Glu	Ala	Glu	Pro	Glu	Pro	Ala	
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gaa	gaa	tac	act	gaa	caa	agt	gaa	gtt	gaa	tca	aca	gag	tat	gta	aat	912
Glu	Glu	Tyr	Thr	Glu	Gln	Ser	Glu	Val	Glu	Ser	Thr	Glu	Tyr	Val	Asn	
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Arg	Gln	Phe	Met	Ala	Glu	Thr	Gln	Phe	Ser	Ser	Gly	Glu	Lys	Glu	Gln	
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gta	gat	gag	tgg	acg	gtc	gaa	aca	gtg	gag	gtg	gtg	aat	tca	ctc	cag	1008
Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	Gln	
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cag	caa	cct	cag	gct	gcg	tct	cct	tca	gta	cca	gag	ccc	cac	tct	ttg	1056
Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	Leu	
			340					345					350			
act	ccg	gtg	gct	cag	gca	gat	ccc	ctt	gtg	aga	aga	cag	cga	gtc	cag	1104
Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln	
			355				360					365				
gac	ctt	atg	gcg	cag	atg	cag	ggg	ccc	tat	aat	ttc	ata	cag	gat	tca	1152
Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Tyr	Asn	Phe	Ile	Gln	Asp	Ser	
			370			375					380					
atg	ctg	gat	ttt	gaa	aac	cag	aca	ctc	gat	cct	gcc	att	gta	tct	gca	1200
Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	Pro	Ala	Ile	Val	Ser	Ala	
385					390					395					400	
cag	cct	atg	aat	ccg	aca	caa	aac	atg	gac	atg	ccc	cag	ctg	gtt	tgc	1248
Gln	Pro	Met	Asn	Pro	Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	Cys	
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cct	cca	gtt	cat	tct	gaa	tct	aga	ctt	gct	caa	cct	aat	caa	gtt	cct	1296
Pro	Pro	Val	His	Ser	Glu	Ser	Arg	Leu	Ala	Gln	Pro	Asn	Gln	Val	Pro	
			420					425					430			
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Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	Glu	
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Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	Thr	Glu	
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Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser	
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gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc	1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe	
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Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys	
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Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln	
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Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr	
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Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser	
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Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln	
675 680 685	
agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc	2112
Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro	
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aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa	2154

Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
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Gly	Ala	Ala	Gly	Ala	Ala	Gly	Ala	Gly	Ala	Ala	Ala	Pro	Ala	Ser	Gln
		35					40					45			

His	Pro	Ala	Thr	Gly	Thr	Gly	Ala	Val	Gln	Thr	Glu	Ala	Met	Lys	Gln
	50					55					60				

Ile	Leu	Gly	Val	Ile	Asp	Lys	Lys	Leu	Arg	Asn	Leu	Glu	Lys	Lys	Lys
65					70					75					80

Gly	Lys	Leu	Asp	Asp	Tyr	Gln	Glu	Arg	Met	Asn	Lys	Gly	Glu	Arg	Leu
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Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	Ser	Lys	Tyr	Gln	Glu	Val	Thr	Asn
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Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg	Ser	Phe	Met	Ala	Leu	Ser
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Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	Lys	Thr	Ala	Arg	Arg	Glu	Gln	Leu
	130					135					140				

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Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
165 170 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
180 185 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
195 200 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
210 215 220

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

Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
245 250 255

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
260 265 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
275 280 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
290 295 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305 310 315 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
325 330 335

Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
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Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
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Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
370 375 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385 390 395 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
405 410 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
420 425 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
435 440 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
450 455 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465 470 475 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
485 490 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
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Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
515 520 525

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
530 535 540

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545 550 555 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
565 570 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
580 585 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser

595

600

605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
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645 650 655

Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly
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Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala
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Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Pro Ala Ser Gln
35 40 45
cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag 192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
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ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu 85 90 95	288
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atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu 145 150 155 160	480
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	530					535					540						
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Gln	Gln	Asn	Gln	Tyr	Gln	Ala	Ser	Tyr	Asn	Gln	Ser	Phe	Ser	Ser	Gln		
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cct	cac	caa	gta	gaa	caa	aca	gac	ctt	cag	caa	gaa	cag	ctt	caa	aca		1728
Pro	His	Gln	Val	Glu	Gln	Thr	Asp	Leu	Gln	Gln	Glu	Gln	Leu	Gln	Thr		
				565					570					575			
gtg	gtt	ggc	act	tac	cat	ggc	tcc	cag	gac	cag	ccc	cac	caa	gtg	act		1776
Val	Val	Gly	Thr	Tyr	His	Gly	Ser	Gln	Asp	Gln	Pro	His	Gln	Val	Thr		
			580					585					590				
ggc	aac	cat	cag	cag	cct	ccc	cag	cag	aac	act	gga	ttt	cca	cgt	agc		1824
Gly	Asn	His	Gln	Gln	Pro	Pro	Gln	Gln	Asn	Thr	Gly	Phe	Pro	Arg	Ser		
		595					600					605					
agt	cag	ccc	tat	tac	aat	agt	cgt	ggc	gtg	tct	cgt	ggc	ggc	tcc	cgt		1872
Ser	Gln	Pro	Tyr	Tyr	Asn	Ser	Arg	Gly	Val	Ser	Arg	Gly	Gly	Ser	Arg		
	610					615					620						
ggc	gct	aga	ggc	tta	atg	aat	gga	tac	agg	ggc	cct	gcc	aat	gga	ttc		1920
Gly	Ala	Arg	Gly	Leu	Met	Asn	Gly	Tyr	Arg	Gly	Pro	Ala	Asn	Gly	Phe		
625					630				635					640			
aga	gga	gga	tat	gat	ggc	tac	cgc	cct	tca	ttc	tct	aac	act	cca	aac		1968
Arg	Gly	Gly	Tyr	Asp	Gly	Tyr	Arg	Pro	Ser	Phe	Ser	Asn	Thr	Pro	Asn		
				645					650					655			
agt	ggc	tat	aca	cag	tct	cag	ttc	agt	gct	ccc	cgg	gac	tac	tct	ggc		2016
Ser	Gly	Tyr	Thr	Gln	Ser	Gln	Phe	Ser	Ala	Pro	Arg	Asp	Tyr	Ser	Gly		
			660					665					670				
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Tyr	Gln	Arg	Asp	Gly	Tyr	Gln	Gln	Asn	Phe	Lys	Arg	Gly	Ser	Gly	Gln		
		675					680					685					
agt	gga	cca	cgg	gga	gcc	cca	cga	ggc	aat	att	ttg	tgg	tgg	tga			2109
Ser	Gly	Pro	Arg	Gly	Ala	Pro	Arg	Gly	Asn	Ile	Leu	Trp	Trp				
	690					695					700						
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 <212> PRT
 <213> Canis familiaris

<400> 10

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

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

His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
50 55 60

Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65 70 75 80

Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
85 90 95

Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
100 105 110

Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
115 120 125

Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
130 135 140

Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145 150 155 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
165 170 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
180 185 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
195 200 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
210 215 220

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

Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
245 250 255

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
260 265 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
275 280 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
290 295 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln

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Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	Gln
				325					330					335	
Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	Leu
			340					345					350		
Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln
		355					360					365			
Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Tyr	Asn	Phe	Ile	Gln	Asp	Ser
	370					375					380				
Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	Pro	Ala	Ile	Val	Ser	Ala
385					390					395					400
Gln	Pro	Met	Asn	Pro	Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	Cys
				405					410					415	
Pro	Pro	Val	His	Ser	Glu	Ser	Arg	Leu	Ala	Gln	Pro	Asn	Gln	Val	Pro
			420					425					430		
Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	Glu
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Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	Thr	Glu
	450					455					460				
Gln	Arg	Pro	Gln	Lys	Glu	Pro	Ile	Asp	Gln	Ile	Gln	Ala	Thr	Ile	Ser
465					470					475					480
Leu	Asn	Thr	Asp	Gln	Thr	Thr	Ala	Ser	Ser	Ser	Leu	Pro	Ala	Ala	Ser
				485					490					495	
Gln	Pro	Gln	Val	Phe	Gln	Ala	Gly	Thr	Ser	Lys	Pro	Leu	His	Ser	Ser
			500					505					510		
Gly	Ile	Asn	Val	Asn	Ala	Ala	Pro	Phe	Gln	Ser	Met	Gln	Thr	Val	Phe
		515					520					525			
Asn	Met	Asn	Ala	Pro	Val	Pro	Pro	Val	Asn	Glu	Pro	Glu	Thr	Leu	Lys
	530					535					540				

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545 550 555 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
565 570 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
580 585 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
595 600 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
610 615 620

Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625 630 635 640

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

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

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

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

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1 5 10 15

48

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

Leu	Lys	Glu	Ile	Val	Glu	Arg	Val	Phe	Gln	Ser	Asn	Tyr	Phe	Asp	Ser	
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act	cac	aac	cac	cag	aat	ggg	cta	tgt	gag	gaa	gaa	gag	gca	gcc	tca	816
Thr	His	Asn	His	Gln	Asn	Gly	Leu	Cys	Glu	Glu	Glu	Glu	Ala	Ala	Ser	
			260					265					270			
gca	cct	aca	gtt	gaa	gac	cag	gta	gct	gaa	gct	gag	cct	gag	cca	gca	864
Ala	Pro	Thr	Val	Glu	Asp	Gln	Val	Ala	Glu	Ala	Glu	Pro	Glu	Pro	Ala	
		275					280					285				
gaa	gaa	tac	act	gaa	caa	agt	gaa	gtt	gaa	tca	aca	gag	tat	gta	aat	912
Glu	Glu	Tyr	Thr	Glu	Gln	Ser	Glu	Val	Glu	Ser	Thr	Glu	Tyr	Val	Asn	
	290					295					300					
aga	caa	ttt	atg	gca	gaa	aca	cag	ttc	agc	agt	ggc	gaa	aag	gag	cag	960
Arg	Gln	Phe	Met	Ala	Glu	Thr	Gln	Phe	Ser	Ser	Gly	Glu	Lys	Glu	Gln	
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Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	Gln	
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cag	caa	cct	cag	gct	gcg	tct	cct	tca	gta	cca	gag	ccc	cac	tct	ttg	1056
Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	Leu	
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act	ccg	gtg	gct	cag	gca	gat	ccc	ctt	gtg	aga	aga	cag	cga	gtc	cag	1104
Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln	
		355					360					365				
gac	ctt	atg	gcg	cag	atg	cag	ggg	ccc	tat	aat	ttc	ata	cag	gat	tca	1152
Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Tyr	Asn	Phe	Ile	Gln	Asp	Ser	
	370					375					380					
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Gln	Pro	Met	Asn	Pro	Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	Cys	
				405					410					415		
cct	cca	gtt	cat	tct	gaa	tct	aga	ctt	gct	caa	cct	aat	caa	gtt	cct	1296
Pro	Pro	Val	His	Ser	Glu	Ser	Arg	Leu	Ala	Gln	Pro	Asn	Gln	Val	Pro	
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Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	Glu	
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tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct				1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser	485	490	495	
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Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser	500	505	510	
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Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe	515	520	525	
aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa				1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys	530	535	540	
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Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln	545	550	555	560
cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca				1728
Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr	565	570	575	
gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act				1776
Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr	580	585	590	
ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc				1824
Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser	595	600	605	
agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt				1872
Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg	610	615	620	
ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc				1920
Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe	625	630	635	640
aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac				1968
Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn	645	650	655	
agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc				2016
Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly	660	665	670	
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Tyr Gln Arg Gly Cys Arg Lys	675			
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<212> PRT
<213> Canis familiaris

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

His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
50 55 60

Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65 70 75 80

Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
85 90 95

Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
100 105 110

Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
115 120 125

Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
130 135 140

Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145 150 155 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
165 170 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
180 185 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
195 200 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
210 215 220

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

Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
245 250 255

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
260 265 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
275 280 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
290 295 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305 310 315 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
325 330 335

Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
340 345 350

Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln
355 360 365

Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
370 375 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
385 390 395 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
405 410 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
420 425 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
435 440 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
450 455 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465 470 475 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
485 490 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
500 505 510

Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
515 520 525

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
530 535 540

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
545 550 555 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
565 570 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
580 585 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
595 600 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
610 615 620

Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625 630 635 640

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

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

Tyr Gln Arg Gly Cys Arg Lys
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<210> 13
<211> 2281
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
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ccg Pro	ccg Pro	ccc Pro	ccg Pro 20	tcg Ser	ggt Gly	tcc Ser	tcc Ser	ggg Gly 25	agc Ser	gag Glu	gcg Ala	gcg Ala	gcg Ala 30	gcg Ala	gcg Ala	96
ggg Gly	gcg Ala	gcg Ala 35	ggg Gly	gcg Ala	gcg Ala	ggg Gly	gcc Ala 40	ggg Gly	gcg Ala	gct Ala	gcg Ala	ccc Pro 45	gcc Ala	tcc Ser	cag Gln	144
cac His	ccc Pro 50	gcg Ala	acc Thr	ggc Gly	acc Thr	ggc Gly 55	gct Ala	gtc Val	cag Gln	acc Thr	gag Glu 60	gcc Ala	atg Met	aag Lys	cag Gln	192
atc Ile 65	ctc Leu	ggg Gly	gtg Val	atc Ile	gac Asp 70	aag Lys	aaa Lys	ctc Leu	cgg Arg	aac Asn 75	ctg Leu	gag Glu	aag Lys	aaa Lys	aag Lys 80	240
ggc Gly	aag Lys	ctt Leu	gat Asp	gat Asp 85	tac Tyr	cag Gln	gaa Glu	cga Arg	atg Met 90	aac Asn	aaa Lys	ggg Gly	gaa Glu	agg Arg 95	ctt Leu	288
aat Asn	caa Gln	gat Asp	cag Gln 100	ctg Leu	gat Asp	gcc Ala	gta Val	tct Ser 105	aag Lys	tac Tyr	cag Gln	gaa Glu	gtc Val 110	aca Thr	aat Asn	336
aac Asn	ttg Leu	gag Glu 115	ttt Phe	gca Ala	aaa Lys	gaa Glu	tta Leu 120	cag Gln	agg Arg	agt Ser	ttc Phe	atg Met 125	gca Ala	tta Leu	agt Ser	384
caa Gln	gat Asp 130	att Ile	cag Gln	aaa Lys	aca Thr	ata Ile 135	aag Lys	aag Lys	act Thr	gca Ala	cgt Arg 140	cgg Arg	gag Glu	cag Gln	ctt Leu	432
atg Met 145	aga Arg	gag Glu	gaa Glu	gcg Ala	gaa Glu 150	caa Gln	aaa Lys	cgt Arg	tta Leu	aaa Lys 155	act Thr	gta Val	ctt Leu	gag Glu	ctc Leu 160	480
cag Gln	tat Tyr	gtt Val	ttg Leu	gac Asp 165	aaa Lys	ttg Leu	gga Gly	gat Asp	gat Asp 170	gaa Glu	gtg Val	aga Arg	act Thr	gac Asp 175	ctg Leu	528
aag Lys	caa Gln	ggt Gly	ttg Leu 180	aat Asn	gga Gly	gtg Val	cca Pro	ata Ile 185	ttg Leu	tot Ser	gaa Glu	gaa Glu	gaa Glu 190	ttg Leu	tcg Ser	576
ttg Leu	ttg Leu	gat Asp 195	gaa Glu	ttc Phe	tac Tyr	aaa Lys	tta Leu 200	gca Ala	gac Asp	cct Pro	gaa Glu	cgg Arg 205	gac Asp	atg Met	agc Ser	624
ttg Leu	agg Arg 210	ttg Leu	aat Asn	gag Glu	cag Gln	tat Tyr 215	gaa Glu	cat His	got Ala	tcc Ser	att Ile 220	cac His	ctg Leu	tgg Trp	gac Asp	672

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

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu 450 455 460	1392
caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser 465 470 475 480	1440
tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser 485 490 495	1488
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aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys 530 535 540	1632
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aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn 645 650 655	1968
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Ser	Gly	Pro	Arg	Gly	Ala	Pro	Arg	Gly	Arg	Gly	Gly	Pro	Pro	Arg	Pro		
		690				695					700						
aac	aga	ggg	atg	ccg	caa	atg	aac	act	cag	caa	gtg	aat	taa				2154
Asn	Arg	Gly	Met	Pro	Gln	Met	Asn	Thr	Gln	Gln	Val	Asn					
		705				710					715						
tctgattcac	aggattatgt	ttaaacgcca	aaaacacact	ggccagtgtgta	ccataatatg												2214
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 <212> PRT
 <213> Canis familiaris

<400> 14

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			20					25					30				

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

His	Pro	Ala	Thr	Gly	Thr	Gly	Ala	Val	Gln	Thr	Glu	Ala	Met	Lys	Gln		
	50					55					60						

Ile	Leu	Gly	Val	Ile	Asp	Lys	Lys	Leu	Arg	Asn	Leu	Glu	Lys	Lys	Lys		
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Gly	Lys	Leu	Asp	Asp	Tyr	Gln	Glu	Arg	Met	Asn	Lys	Gly	Glu	Arg	Leu		
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Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	Ser	Lys	Tyr	Gln	Glu	Val	Thr	Asn		
			100					105					110				

Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg	Ser	Phe	Met	Ala	Leu	Ser		
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Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145 150 155 160

Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
165 170 175

Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
180 185 190

Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
195 200 205

Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
210 215 220

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

Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
245 250 255

Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
260 265 270

Ala Pro Thr Val Glu Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala
275 280 285

Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn
290 295 300

Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305 310 315 320

Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
325 330 335

Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu
340 345 350

Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln

355

360

365

Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser
 370 375 380

Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala
 385 390 395 400

Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys
 405 410 415

Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro
 420 425 430

Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
 435 440 445

Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
 450 455 460

Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
 465 470 475 480

Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
 485 490 495

Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
 500 505 510

Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
 515 520 525

Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
 530 535 540

Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
 545 550 555 560

Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr
 565 570 575

Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr
 580 585 590

Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser
595 600 605

Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg
610 615 620

Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe
625 630 635 640

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

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

Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln
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690 695 700

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<212> DNA
<213> Bos taurus

<220>
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<222> (82).. (2208)

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

ggc agc aag tcg tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg aat 159
Gly Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Asn
15 20 25

gag gcg ggg gcc ggg gcc gcc gcg ccg gct tcc caa cac ccc atg acc 207
Glu Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Met Thr

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atc Ile	gac Asp 60	aag Lys	aaa Lys	ctt Leu	cgg Arg	aac Asn 65	ctg Leu	gag Glu	aag Lys	aaa Lys	aag Lys 70	ggc Gly	aag Lys	ctt Leu	gat Asp	303
gat Asp 75	tat Tyr	cag Gln	gaa Glu	cga Arg	atg Met 80	aac Asn	aaa Lys	ggg Gly	gaa Glu	agg Arg 85	ctt Leu	aat Asn	caa Gln	gat Asp	cag Gln 90	351
ctg Leu	gat Asp	gcc Ala	gtg Val	tct Ser 95	aag Lys	tac Tyr	cag Gln	gaa Glu	gtc Val 100	aca Thr	aat Asn	aac Asn	ttg Leu	gag Glu 105	ttt Phe	399
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aaa Lys	aca Thr	ata Ile 125	aag Lys	aag Lys	aca Thr	gca Ala	cgt Arg 130	cgg Arg	gag Glu	cag Gln	ctt Leu	atg Met 135	aga Arg	gag Glu	gaa Glu	495
gct Ala	gaa Glu 140	cag Gln	aaa Lys	cgt Arg	tta Leu	aaa Lys 145	aca Thr	gta Val	ctt Leu	gag Glu	ctg Leu 150	cag Gln	tat Tyr	gtt Val	ttg Leu	543
gac Asp 155	aaa Lys	cta Leu	gga Gly	gat Asp	gat Asp 160	gaa Glu	gtg Val	aga Arg	act Thr	gac Asp 165	ctg Leu	aag Lys	caa Gln	ggt Gly	ttg Leu 170	591
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aag Lys	gaa Glu 220	aaa Lys	cct Pro	gta Val	tgt Cys	gga Gly 225	aca Thr	act Thr	tat Tyr	aaa Lys	gct Ala 230	cta Leu	aag Lys	gaa Glu	att Ile	783
gtt Val 235	gag Glu	cgt Arg	gtt Val	ttc Phe	cag Gln 240	tca Ser	aac Asn	tac Tyr	ttt Phe	gac Asp 245	agc Ser	acc Thr	cac His	aac Asn	cac His 250	831
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cag act aca gca tca tca tcc ctt cct gct gct tct cag cct caa gtg Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val 475 480 485 490	1551

ttc cag gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val 495 500 505	1599
aat gca gct cca ttc caa tcc atg caa acg gta ttc aat atg aat gcc Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala 510 515 520	1647
cca gtt cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln 525 530 535	1695
tac cag gcc agt tac aac cag agc ttt tcc agt cag cct cac caa gta Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val 540 545 550	1743
gaa caa aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act Glu Gln Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr 555 560 565 570	1791
tat cat ggt tct cag gac cag ccc cat caa gtg act ggt aac cac cag Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr Gly Asn His Gln 575 580 585	1839
cag cct cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr 590 595 600	1887
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gat ggt tac cgc cct tca ttc tct act aac act cca aac agt ggt tat Asp Gly Tyr Arg Pro Ser Phe Ser Thr Asn Thr Pro Asn Ser Gly Tyr 635 640 645 650	2031
aca caa tct caa ttc agt gct ccc cgg gac tac tct ggc tat cag cgg Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg 655 660 665	2079
gat gga tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro 670 675 680	2127
cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly 685 690 695	2175
atg ccg caa atg aac act cag caa gtg aat taa tctgattcac aggattatgt Met Pro Gln Met Asn Thr Gln Gln Val Asn 700 705	2228
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gttttgtaag gattggtagt aaatatcatt ccttatgacg tacattgtct gtcactaatc	3068
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aatcataaca ctcttggtta catgtttttc ctgcagcctg aaagttttta taagaaaaag	3188
acatcaaatg cctgctgctg ccaccctttt aaattgctat cttttgaaaa gcaccagtat	3248
gtgttttaga ttgatttccc tatttttaggg aaatgacagt cagtagtttc acttctgatg	3308
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aaaaaaaaaa aaaaaaaa	3386

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 <213> Bos taurus

<400> 16

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			20					25					30		

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

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

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

Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys
85 90 95

Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
100 105 110

Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
115 120 125

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

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145 150 155 160

Glu Val Arg Thr Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu
165 170 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp
180 185 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
195 200 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
210 215 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225 230 235 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
245 250 255

Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Ala Ala Glu
260 265 270

Ala Glu Pro Glu Pro Val Glu Glu Tyr Thr Glu Gln Asn Glu Val Glu
275 280 285

Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
290 295 300

Ser Gly Glu Lys Glu Gln Val Asp Asp Trp Thr Val Glu Thr Val Glu
305 310 315 320

Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
325 330 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val
340 345 350

Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
355 360 365

Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
370 375 380

Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Ala Gln Asn Met Asp
385 390 395 400

Ile Pro Gln Leu Val Cys Pro Pro Val His Ser Glu Ser Arg Leu Ala
405 410 415

Gln Pro Asn Gln Val Ser Val Gln Pro Glu Ala Thr Gln Val Pro Leu
420 425 430

Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
435 440 445

Pro Ser His Ala Thr Asp Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln
450 455 460

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465 470 475 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
485 490 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
500 505 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn
515 520 525

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

Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545 550 555 560

Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
565 570 575

Gln Pro His Gln Val Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn
580 585 590

Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn Ser Arg Gly Val
595 600 605

Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
610 615 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625 630 635 640

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

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

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

Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr
690 695 700

Gln Gln Val Asn
705

<210> 17

<211> 3150
 <212> DNA
 <213> Equus caballus

<220>
 <221> CDS
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 Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val
 20 25 30
 aca aat aac ttg gag ttt gcg aaa gaa ttg cag agg agt ttc atg gcg 144
 Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala
 35 40 45
 ttg agt cag gat att cag aaa aca ata aag aag acg gca cgt cgg gag 192
 Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu
 50 55 60
 cag ctt atg aga gaa gaa gct gaa cag aaa cgt tta aaa act gta ctt 240
 Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu
 65 70 75 80
 gag ctg cag tat gtt ttg gac aaa ttg gga gat gaa gaa gtg cga act 288
 Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Glu Glu Val Arg Thr
 85 90 95
 gac ctg aaa caa ggt ttg aat gga gtg cca ata ctc tct gaa gaa gag 336
 Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu
 100 105 110
 ttg tcg ctg ttg gat gag ttc tac aag tta gca gac cct gta cgg gac 384
 Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Val Arg Asp
 115 120 125
 atg agc ttg agg ttg aat gag cag tat gag cat gcc tcc att cac ctg 432
 Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu
 130 135 140
 tgg gac ttg ctg gaa ggg aag gaa aaa tct gtc tgt gga aca acc tat 480
 Trp Asp Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr
 145 150 155 160
 aaa gct ctg agg gaa att gtt gag cgt gtt ttc cag tcc aac tac ttt 528
 Lys Ala Leu Arg Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe
 165 170 175
 gac agc acc cac aac cac cag aat ggg ctc tgt gag gag gaa gag gct 576
 Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala
 180 185 190

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

tct cag cct cag gtg ttc cag gct ggg aca agc aaa cct tta cac agc Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser 420 425 430	1296
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ttc aac atg aat gcc ccg gtt cct cct gtt aat gaa cca gaa act tta Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu 450 455 460	1392
aaa cag caa aat cag tac cag gcc agc tat aac cag agc ttt tcc agt Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser 465 470 475 480	1440
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acg gtg gtt ggt act tac cat gct tcc caa gac cag ccc cat caa gtg Thr Val Val Gly Thr Tyr His Ala Ser Gln Asp Gln Pro His Gln Val 500 505 510	1536
acc ggt aac cac cag cag cct ccc cag cag aac act ggg ttt cca cgt Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg 515 520 525	1584
agc agt cag ccc tat tac aac agt cgt ggt gtg tct cgt gga ggc tcc Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser 530 535 540	1632
cgt ggt gct aga ggc ttg atg aat gga tac agg ggc cct gcc aat gga Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly 545 550 555 560	1680
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cag agt gga ccc cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg 610 615 620	1872
ccc aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn 625 630 635	1917
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 <211> 638
 <212> PRT
 <213> Equus caballus

<400> 18

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Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala
35 40 45

Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu
50 55 60

Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu
65 70 75 80

Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Glu Glu Val Arg Thr
85 90 95

Asp Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu
100 105 110

Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Val Arg Asp
115 120 125

Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu
130 135 140

Trp Asp Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr
145 150 155 160

Lys Ala Leu Arg Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe
165 170 175

Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala
180 185 190

Thr Ser Ala Pro Thr Ala Glu Asp Gln Gly Ala Glu Ala Glu Pro Glu
195 200 205

Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr
210 215 220

Val Asn Arg Gln Phe Met Ala Glu Ala Gln Phe Ser Gly Glu Lys Glu
225 230 235 240

Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu
245 250 255

Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser

260	265	270
Leu Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val		
275	280	285
Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp		
290	295	300
Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser		
305	310	315
Ala Gln Pro Met Asn Pro Ala Gln Asn Met Asp Met Pro Gln Leu Val		
325	330	335
Cys Pro Pro Val His Ala Glu Ser Arg Leu Ala Gln Pro Asn Gln Val		
340	345	350
Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser		
355	360	365
Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr		
370	375	380
Glu Gln Arg Pro Gln Lys Glu Pro Thr Asp Gln Ile Gln Ala Thr Ile		
385	390	395
Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala		
405	410	415
Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser		
420	425	430
Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val		
435	440	445
Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu		
450	455	460
Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser		
465	470	475
Pro Pro His Gln Val Glu Gln Thr Glu Leu Pro Gln Glu Gln Leu Gln		
485	490	495

Thr Val Val Gly Thr Tyr His Ala Ser Gln Asp Gln Pro His Gln Val
500 505 510

Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
515 520 525

Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
530 535 540

Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
545 550 555 560

Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
565 570 575

Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser
580 585 590

Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
595 600 605

Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
610 615 620

Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
625 630 635

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<211> 6181
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (179).. (2302)

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ccacccttgc cccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg 178
atg ccc tcg gcc acc agc cac agc gga agc ggc agc aaa tcg tcg gga 226
Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly

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ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag gcg gcg gcc ggg gca	274			
Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala				
20 25 30				
gct gcg ccg gct tct cag cat ccg gca acc ggc acc ggc gcc gtc cag	322			
Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln				
35 40 45				
acc gag gcc atg aag cag att ctc ggc gta atc gac aag aaa ctt cgg	370			
Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg				
50 55 60				
aac ctg gag aag aaa aag ggt aaa ctt gat gat tac cag gaa cga atg	418			
Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met				
65 70 75 80				
aat aaa ggg gaa agg ctc aat caa gac cag ctg gat gcc gta tct aag	466			
Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys				
85 90 95				
tac cag gaa gtc aca aat aat ttg gag ttt gca aag gaa tta cag agg	514			
Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg				
100 105 110				
agt ttc atg gca tta agt caa gat att cag aaa aca ata aag aag aca	562			
Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr				
115 120 125				
gca cgt cgg gaa cag ctt atg aga gaa gaa gca gaa cag aag cgc tta	610			
Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu				
130 135 140				
aaa act gta ctt gag tta cag tat gta ttg gat aag ctg gga gat gat	658			
Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp				
145 150 155 160				
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Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg
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Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
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acc	cag	aac	atg	gat	atg	cct	cag	ctg	gtt	tgc	cct	cag	gtt	cat	tct	1371
Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	Cys	Pro	Gln	Val	His	Ser	
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gaa	tct	aga	ctt	gcc	caa	tct	aat	caa	gtt	cct	gta	caa	cca	gaa	gcc	1419
Glu	Ser	Arg	Leu	Ala	Gln	Ser	Asn	Gln	Val	Pro	Val	Gln	Pro	Glu	Ala	
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aca	cag	gtt	cct	ttg	gtt	tca	tcc	aca	agt	gag	ggg	tat	aca	gca	tct	1467
Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	Glu	Gly	Tyr	Thr	Ala	Ser	
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Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	Thr	Glu	Gln	Arg	Pro	Gln	Lys	
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gag	cca	atg	gat	cag	att	cag	gca	aca	ata	tct	ttg	aat	aca	gac	cag	1563
Glu	Pro	Met	Asp	Gln	Ile	Gln	Ala	Thr	Ile	Ser	Leu	Asn	Thr	Asp	Gln	

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act aca gca tcc tca tcc ctt cct gct gct tct cag cct caa gtg ttc				1611
Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe	480	485	490	
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Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn	495	500	505	
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Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro	510	515	520	
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Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr	525	530	535	
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Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu	545	550	555	
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Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr	560	565	570	
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His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln	575	580	585	
ccc cca cag cag aac act ggc ttt cca cgt agc agt cag cct tat tac				1947
Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr	590	595	600	
aac agt cgt ggg gta tct cga gga ggg tct cgt ggt gcc aga ggc ttg				1995
Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu	605	610	615	
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Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp	625	630	635	
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Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln	640	645	650	
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Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly	655	660	665	
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Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly	670	675	680	
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Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro	685	690	695	

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Gln Met Asn Thr Gln Gln Val Asn	
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Ala	Ala	Pro	Ala	Ser	Gln	His	Pro	Ala	Thr	Gly	Thr	Gly	Ala	Val	Gln
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Thr	Glu	Ala	Met	Lys	Gln	Ile	Leu	Gly	Val	Ile	Asp	Lys	Lys	Leu	Arg
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Asn	Leu	Glu	Lys	Lys	Lys	Gly	Lys	Leu	Asp	Asp	Tyr	Gln	Glu	Arg	Met
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Asn	Lys	Gly	Glu	Arg	Leu	Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	Ser	Lys
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Tyr	Gln	Glu	Val	Thr	Asn	Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg
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Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
115 120 125

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

Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145 150 155 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
165 170 175

Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
180 185 190

Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
195 200 205

Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
210 215 220

Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225 230 235 240

Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
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Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
260 265 270

Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
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Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
290 295 300

Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
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Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
325 330 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val

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Ser	Met	Gln	Thr	Val	Phe	Asn	Met	Asn	Ala	Pro	Val	Pro	Pro	Ala	Asn						
		515					520					525									
Glu	Pro	Glu	Thr	Leu	Lys	Gln	Gln	Ser	Gln	Tyr	Gln	Ala	Thr	Tyr	Asn						
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Gln	Asp	Gln	Leu	Gln	Thr	Val	Val	Gly	Thr	Tyr	His	Gly	Ser	Gln	Asp						
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Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
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Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
595 600 605

Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
610 615 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625 630 635 640

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

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

Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg
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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly
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agc Ser	aaa Lys	tcg Ser	tcg Ser	gga Gly	ccg Pro	ccg Pro	ccg Pro	ccg Pro	tcc Ser	ggt Gly	tcc Ser	tcc Ser	ggg Gly	agt Ser	gag Glu	219
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30 35 40																
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60 65 70 75																
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80 85 90																
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95 100 105																
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Ser	Ala	Gln	Pro	Met	Asn	Pro	Thr	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	
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Val	Pro	Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	
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agt	gag	ggg	tat	aca	gca	tct	cag	ccc	ttg	tac	cag	cca	tct	cat	gct	1467
Ser	Glu	Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	
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acg	gag	cag	cgg	ccg	cag	aaa	gag	cca	atg	gat	cag	att	cag	gca	aca	1515
Thr	Glu	Gln	Arg	Pro	Gln	Lys	Glu	Pro	Met	Asp	Gln	Ile	Gln	Ala	Thr	
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ata	tct	ttg	aat	aca	gac	cag	act	aca	gca	tcc	tca	tcc	ctt	cct	gct	1563
Ile	Ser	Leu	Asn	Thr	Asp	Gln	Thr	Thr	Ala	Ser	Ser	Ser	Leu	Pro	Ala	

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Ala Ser Gln Pro Gln	Val Phe Gln Ala Gly	Thr Ser Lys Pro Leu	His	
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agc agt gga atc aat	gta aat gca gct cca	ttc cag tcc atg caa	acg	1659
Ser Ser Gly Ile Asn	Val Asn Ala Ala Pro	Phe Gln Ser Met Gln	Thr	
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gtg ttc aat atg aat	gct cca gtc cct cct	gct aat gaa cca gaa	acg	1707
Val Phe Asn Met Asn	Ala Pro Val Pro Pro	Ala Asn Glu Pro Glu	Thr	
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tta aaa caa cag agt	cag tac cag gcc act	tat aac cag agt ttt	tcc	1755
Leu Lys Gln Gln Ser	Gln Tyr Gln Ala Thr	Tyr Asn Gln Ser Phe	Ser	
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agt cag cct cac caa	gtg gaa caa aca gag	ctt caa caa gac caa	ctg	1803
Ser Gln Pro His Gln	Val Glu Gln Thr Glu	Leu Gln Gln Asp Gln	Leu	
	545	550	555	
caa acg gtg gtt ggc	act tac cat gga tcc	cag gac cag cct cat	caa	1851
Gln Thr Val Val Gly	Thr Tyr His Gly Ser	Gln Asp Gln Pro His	Gln	
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Val Pro Gly Asn His	Gln Gln Pro Pro Gln	Gln Asn Thr Gly Phe	Pro	
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Arg Ser Ser Gln Pro	Tyr Tyr Asn Ser Arg	Gly Val Ser Arg Gly	Gly	
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Gly Phe Arg Gly Gly	Tyr Asp Gly Tyr Arg	Pro Ser Phe Ser Asn	Thr	
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cca aac agt ggt tat	tca cag tct cag ttc	act gct ccc cgg gac	tac	2091
Pro Asn Ser Gly Tyr	Ser Gln Ser Gln Phe	Thr Ala Pro Arg Asp	Tyr	
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Ser Gly Tyr Gln Arg	Asp Gly Tyr Gln Gln	Asn Phe Lys Arg Gly	Ser	
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Gly Gln Ser Gly Pro	Arg Gly Ala Pro Arg	Gly Arg Gly Gly Pro	Pro	
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Arg Pro Asn Arg Gly	Met Pro Gln Met Asn	Thr Gln Gln Val Asn		
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Ala	Ala	Pro	Ala	Ser	Gln	His	Pro	Ala	Thr	Gly	Thr	Gly	Ala	Val	Gln
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Thr	Glu	Ala	Met	Lys	Gln	Ile	Leu	Gly	Val	Ile	Asp	Lys	Lys	Leu	Arg
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Tyr	Gln	Glu	Val	Thr	Asn	Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg
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Ser	Phe	Met	Ala	Leu	Ser	Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	Lys	Thr
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Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp
145 150 155 160

Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
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Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
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Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
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Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
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Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
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Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
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Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
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Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
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Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
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Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
325 330 335

Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
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Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr

355

360

365

Asn Phe Ile Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met
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Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val
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His Ser Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro
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Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr
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Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro
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Gln Lys Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr
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Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln
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Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn
 485 490 495

Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn
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Ala Pro Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser
 515 520 525

Gln Tyr Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln
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Val Glu Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly
 545 550 555 560

Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His
 565 570 575

Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro
 580 585 590

Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg
595 600 605

Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly
610 615 620

Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr
625 630 635 640

Ser Gln Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg
645 650 655

Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro
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Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly
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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
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Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln

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aac	ctg	gag	aag	aaa	aag	ggt	aaa	ctt	gat	gat	tac	cag	gaa	cga	atg	418
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Tyr	Gln	Glu	Val	Thr	Asn	Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg	
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Ser	Phe	Met	Ala	Leu	Ser	Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	Lys	Thr	
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Lys	Thr	Val	Leu	Glu	Leu	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	Asp	Asp	
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Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
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Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
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Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
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Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu

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Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
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Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
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Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
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Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
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Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
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Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
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Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
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Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
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Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
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Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
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Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
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Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
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Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
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Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
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Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
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Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
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Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
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Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
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Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
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Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
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Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
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Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
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Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
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gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca      459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
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Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
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aca ata aag aag aca gca cgt ccg gaa cag ctt atg aga gaa gaa gca      555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
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Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
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Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
                        160                    165                    170

gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc      699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
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tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag      747

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Ser	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln	Asp	Leu	Met	Ala	Gln		
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Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
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Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
435 440 445

Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
450 455 460

Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465 470 475 480

Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
485 490 495

Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
500 505 510

Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
515 520 525

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

Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545 550 555 560

Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
565 570 575

Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
580 585 590

Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
595 600 605

Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
610 615 620

Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625 630 635 640

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

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

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

Ile Leu Trp Trp
690

<210> 29
<211> 2109
<212> DNA
<213> Gallus gallus

<220>
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<222> (1).. (2109)

<400> 29	
atg ccc tcg gct acc aac ggc acc atg gcg agc agc agc ggg aag gcg	48
Met Pro Ser Ala Thr Asn Gly Thr Met Ala Ser Ser Ser Gly Lys Ala	
1 5 10 15	
ggc ccg ggc ggc aac gag cag gcc ccg gcg gcg gca gcg gcg gcc ccg	96
Gly Pro Gly Gly Asn Glu Gln Ala Pro Ala Ala Ala Ala Ala Pro	
20 25 30	
cag gcg tcg ggc ggc agc atc acc tcg gtt cag acc gag gcc atg aag	144
Gln Ala Ser Gly Gly Ser Ile Thr Ser Val Gln Thr Glu Ala Met Lys	
35 40 45	
cag atc ttg gga gtg atc gac aaa aag ctc cgc aac ctc gag aag aaa	192
Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys	
50 55 60	
aag agc aaa ctt gac gat tac cag gaa cga atg aac aag ggg gaa cgt	240
Lys Ser Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg	
65 70 75 80	
cta aat caa gat caa ctg gat gca gtg tca aaa tac cag gaa gtg aca	288
Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr	
85 90 95	
aat aac ctg gaa ttc gct aaa gaa ctg cag agg agc ttt atg gca ctg	336
Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu	
100 105 110	
agc caa gat atc cag aaa aca ata aaa aag acg gct cgc agg gag cag	384
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln	
115 120 125	
ctg atg aga gaa gag gct gag cag aag cgt tta aag act gtg cta gag	432

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

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

aac agt cag cct tat tac aac agt cgg gga gtg tct cgt ggt gga tca Asn Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser	1824
595 600 605	
cgt ggg act cgt gga ttg atg aat ggt tac agg gga cct gca aat gga Arg Gly Thr Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly	1872
610 615 620	
ttt aga gga gga tat gat ggc tac cgt cct tca ttt tcc aac act ccg Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro	1920
625 630 635 640	
aac agt ggt tac acg cag ccc caa ttt aat gct cct cga gat tat tca Asn Ser Gly Tyr Thr Gln Pro Gln Phe Asn Ala Pro Arg Asp Tyr Ser	1968
645 650 655	
aac tac cag cgg gat gga tat cag cag aac ttc aaa cgt ggt tct gga Asn Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly	2016
660 665 670	
caa agt ggg cct cgg gga gct cct cga ggt cgt gga ggg ccc cca aga Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg	2064
675 680 685	
cca aac aga ggg atg cct caa atg aac gct cag caa gtg aat taa Pro Asn Arg Gly Met Pro Gln Met Asn Ala Gln Gln Val Asn	2109
690 695 700	

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

<400> 30

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

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

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

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

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

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

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

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

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

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

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

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

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

Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
210 215 220

Ala Leu Lys Glu Val Val Glu Arg Ile Leu Gln Thr Ser Tyr Phe Asp
225 230 235 240

Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala
245 250 255

Pro Thr Pro Ala Val Glu Asp Thr Val Ala Glu Ala Glu Pro Asp Pro
260 265 270

Ala Glu Glu Phe Thr Glu Pro Thr Glu Val Glu Ser Thr Glu Tyr Val
275 280 285

Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Ser Glu Lys Glu
290 295 300

Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu

305		310		315		320
Gln Gln Gln Thr	Gln 325	Ala Thr Ser Pro	Pro 330	Val Pro Glu Pro	His 335	Thr
Leu Thr Thr Val	Ala 340	Gln Ala Asp Pro	Leu 345	Val Arg Arg Gln	Arg 350	Val
Gln Asp Leu Met	Ala 355	Gln Met Gln Gly	Pro 360	Tyr Asn Phe Met	Gln 365	Asp
Ser Met Leu Glu	Phe 370	Glu Asn Gln Thr	Leu 375	Asp Pro Ala Ile	Val 380	Ser
Ala Gln Pro Met	Asn 385	Pro Ala Gln Asn	Leu 390	Asp Met Pro Gln	Met 395	Val
Cys Pro Pro Val	His 405	Thr Glu Ser Arg	Leu 410	Ala Gln Pro Asn	Gln 415	Val
Pro Val Gln Pro	Glu 420	Ala Thr Gln Val	Pro 425	Leu Val Ser Ser	Thr 430	Ser
Glu Gly Tyr Thr	Ala 435	Ser Gln Pro Met	Tyr 440	Gln Pro Ser His	Thr 445	Thr
Glu Gln Arg Pro	Gln 450	Lys Glu Ser Ile	Asp 455	Gln Ile Gln Ala	Ser 460	Met
Ser Leu Asn Ala	Asp 465	Gln Thr Pro Ser	Ser 470	Ser Ser Leu Pro	Thr 475	Ala
Ser Gln Pro Gln	Val 485	Phe Gln Ala Gly	Ser 490	Ser Lys Pro Leu	His 495	Ser
Ser Gly Ile Asn	Val 500	Asn Ala Ala Pro	Phe 505	Gln Ser Met Gln	Thr 510	Val
Phe Asn Met Asn	Ala 515	Pro Val Pro Pro	Val 520	Asn Glu Pro Glu	Ala 525	Leu
Lys Gln Gln Asn	Gln 530	Tyr Gln Ala Ser	Tyr 535	Asn Gln Ser Phe	Ser 540	Asn

Gln Pro His Gln Val Glu Gln Ser Asp Leu Gln Gln Glu Gln Leu Gln
545 550 555 560

Thr Val Val Gly Thr Tyr His Gly Ser Pro Asp Gln Thr His Gln Val
565 570 575

Ala Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
580 585 590

Asn Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
595 600 605

Arg Gly Thr Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
610 615 620

Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
625 630 635 640

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

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

Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
675 680 685

Pro Asn Arg Gly Met Pro Gln Met Asn Ala Gln Gln Val Asn
690 695 700

<210> 31
<211> 63
<212> PRT
<213> Homo sapiens

<400> 31

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

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

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

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

<210> 32
<211> 18
<212> PRT
<213> Homo sapiens

<400> 32

Val Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr
1 5 10 15

Leu Lys

<210> 33
<211> 16
<212> PRT
<213> Homo sapiens

<400> 33

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

<210> 34
<211> 25
<212> PRT
<213> Homo sapiens

<400> 34

Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys
1 5 10 15

Lys Gly Lys Leu Asp Asp Tyr Gln Glu
20 25

<210> 35
<211> 23
<212> PRT
<213> Homo sapiens

<400> 35

Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln

1 5 10 15

Met Asn Thr Gln Gln Val Asn
20

<210> 36
<211> 5
<212> PRT
<213> Gallus gallus

<400> 36

Ser Tyr Gln Met Asn
1 5

<210> 37
<211> 17
<212> PRT
<213> Gallus gallus

<400> 37

Ala Ile Asn Lys Phe Gly Asn Ser Thr Gly His Gly Ala Ala Val Lys
1 5 10 15

Gly

<210> 38
<211> 19
<212> PRT
<213> Gallus gallus

<400> 38

His Ala Tyr Gly Tyr Cys Gly Ser Gly Thr Trp Cys Ala Ala Gly Glu
1 5 10 15

Ile Asp Ala

<210> 39
<211> 128
<212> PRT
<213> Gallus gallus

<400> 39

Ala Val Thr Leu Asp Glu Ser Gly Gly Gly Leu Gln Met Ser Arg Gly
1 5 10 15

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

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

Ala Ala Ile Asn Lys Phe Gly Asn Ser Thr Gly His Gly Ala Ala Val
50 55 60

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

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

Thr Lys His Ala Tyr Gly Tyr Cys Gly Ser Gly Thr Trp Cys Ala Ala
100 105 110

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

<210> 40
<211> 9
<212> PRT
<213> Gallus gallus

<400> 40

Ser Gly Gly Gly Ser Tyr Ser Tyr Gly
1 5

<210> 41
<211> 7
<212> PRT
<213> Gallus gallus

<400> 41

Asn Asn Lys Arg Pro Ser Asp
1 5

<210> 42
<211> 10
<212> PRT
<213> Gallus gallus

<400> 42

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

<210> 43

<211> 108

<212> PRT

<213> Gallus gallus

<400> 43

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

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

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

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

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

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

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

<210> 44

<211> 5

<212> PRT

<213> Rabbit

<400> 44

Ser His Ser Leu Gly
1 5

<210> 45

<211> 16

<212> PRT

<213> Rabbit

<400> 45

Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys Gly
1 5 10 15

<210> 46

<211> 13

<212> PRT

<213> Rabbit

<400> 46

Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu
1 5 10

<210> 47

<211> 121

<212> PRT

<213> Homo sapiens

<400> 47

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser His
20 25 30

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

Gly Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys
50 55 60

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

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

Arg Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 48

<211> 13
<212> PRT
<213> Rabbit

<400> 48

Gln Ala Ser Gln Ser Leu Tyr Asn Asn Glu Asn Leu Ala
1 5 10

<210> 49
<211> 7
<212> PRT
<213> Rabbit

<400> 49

Gly Ala Ser Thr Leu Ala Ser
1 5

<210> 50
<211> 13
<212> PRT
<213> Rabbit

<400> 50

Leu Gly Glu Phe Ser Cys Gly Ser Ala Asp Cys Phe Ala
1 5 10

<210> 51
<211> 112
<212> PRT
<213> Homo sapiens

<400> 51

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

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

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

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

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

Cys Glu Asp Phe Ala Ile Tyr Tyr Cys Leu Gly Glu Phe Ser Cys Gly
85 90 95

Ser Ala Asp Cys Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 52
<211> 4
<212> PRT
<213> Gallus gallus

<400> 52

Phe Asp Met Gly
1

<210> 53
<211> 17
<212> PRT
<213> Gallus gallus

<400> 53

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

Gly

<210> 54
<211> 12
<212> PRT
<213> Gallus gallus

<400> 54

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

<210> 55
<211> 120
<212> PRT
<213> Gallus gallus

<400> 55

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

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

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

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

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

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

Thr Arg Gly Ser Gly Tyr Val Gly Ala Gly Ala Ile Asp Ala Trp Gly
100 105 110

His Gly Thr Glu Val Ile Val Ser
115 120

<210> 56
<211> 8
<212> PRT
<213> Gallus gallus

<400> 56

Ser Gly Gly Ser Gly Tyr Tyr Gly
1 5

<210> 57
<211> 7
<212> PRT
<213> Gallus gallus

<400> 57

Asn Asp Lys Arg Pro Ser Asp
1 5

<210> 58
<211> 10
<212> PRT
<213> Gallus gallus

<400> 58

Arg Tyr Asp Ser Thr Asp Ser Gly Ile Phe
1 5 10

<210> 59
<211> 105
<212> PRT
<213> Gallus gallus

<400> 59

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

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

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

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

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

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

Gly Ala Gly Thr Thr Leu Thr Val Leu
100 105

<210> 60
<211> 6
<212> PRT
<213> Oryctolagus cuniculus

<400> 60

Gly Ser Tyr Tyr Met Ser
1 5

<210> 61
<211> 17
<212> PRT
<213> Oryctolagus cuniculus

<400> 61

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

Gly

<210> 62
 <211> 4
 <212> PRT
 <213> Oryctolagus cuniculus

<400> 62

Gly Asn Lys Leu
 1

<210> 63
 <211> 112
 <212> PRT
 <213> Oryctolagus cuniculus

<400> 63

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

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

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

Ala Tyr Ile Tyr Ile Gly Asp Gly Val Thr Ala Tyr Ala Asn Trp Ala
 50 55 60

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

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

Arg Gly Asn Lys Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser
 100 105 110

<210> 64
 <211> 11

<212> PRT
<213> Oryctolagus cuniculus

<400> 64

Gln Ala Ser Gln Ser Ile Ser Ser Tyr Leu Ala
1 5 10

<210> 65
<211> 7
<212> PRT
<213> Oryctolagus cuniculus

<400> 65

Asp Ala Ser Asn Leu Asp Ser
1 5

<210> 66
<211> 14
<212> PRT
<213> Oryctolagus cuniculus

<400> 66

Gln Cys Thr Ala Val Ser Ser Ala Thr Ile Tyr Gly Asn Ala
1 5 10

<210> 67
<211> 112
<212> PRT
<213> Oryctolagus cuniculus

<400> 67

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

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

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

Tyr Asp Ala Ser Asn Leu Asp Ser Gly Val Pro Ser Arg Phe Lys Gly
50 55 60

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

Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Cys Thr Ala Val Ser Ser Ala
85 90 95

Thr Ile Tyr Gly Asn Ala Phe Gly Gly Gly Thr Glu Val Val Val Lys
100 105 110

<210> 68
<211> 127
<212> PRT
<213> Gallus gallus

<400> 68

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

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

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

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

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

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

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

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

<210> 69
<211> 107
<212> PRT
<213> Gallus gallus

<400> 69

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

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

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

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

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

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

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

<210> 70
<211> 148
<212> PRT
<213> Mus musculus

<400> 70

Met Glu Trp Ser Gly Val Phe Ile Phe Leu Leu Ser Gly Thr Ala Gly
1 5 10 15

Val Leu Ser Glu Val Gln Leu His Gln Phe Gly Ala Glu Leu Val Lys
20 25 30

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

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

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

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

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

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

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

Pro Ser Val Tyr
145

<210> 71
<211> 105
<212> PRT
<213> Mus musculus

<400> 71

Gly Leu Phe Cys Ser Val Glu Arg Cys His Tyr Gln Leu Gln Ser Ser
1 5 10 15

Gln Asn Leu Leu Ser Ile Val Asn Arg Tyr His Tyr Met Ser Gly Asn
20 25 30

Pro Pro Lys Leu Leu Val Tyr Pro Ala Leu Leu Ile Tyr Glu Ala Ser
35 40 45

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

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

Phe Tyr Tyr Cys Gln His Asn Arg Gly Ser Phe Leu Pro Ser Ser Ser
85 90 95

Val Gln Val Pro Arg Arg Arg Ser Asn
100 105

<210> 72
<211> 109
<212> PRT
<213> Mus musculus

<400> 72

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

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

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

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

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

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

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

<210> 73
<211> 94
<212> PRT
<213> Mus musculus

<400> 73

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

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

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

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

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

Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gln

85

90

<210> 74
 <211> 118
 <212> PRT
 <213> Mus musculus

<400> 74

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

Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Leu Ile Val Trp Ile Lys Gln
 20 25 30

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

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

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

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

Asp Tyr Tyr Glu Gly Tyr Phe Asp Val Trp Gly Ala Gly Pro Arg His
 100 105 110

Leu Leu Ala Ser Leu Ser
 115

<210> 75
 <211> 107
 <212> PRT
 <213> Mus musculus

<400> 75

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

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

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

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

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

Asn Leu Glu Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln His Tyr Ser
85 90 95

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

<210> 76
<211> 113
<212> PRT
<213> Mus musculus

<400> 76

Gly Ala Glu Leu Val Arg Ser Gly Ala Ser Val Lys Met Ser Cys Lys
1 5 10 15

Ala Ser Gly Tyr Ser Phe Thr Asp Tyr Asn Met Tyr Trp Val Lys Gln
20 25 30

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

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

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

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

Gly Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 77
 <211> 117
 <212> PRT
 <213> Mus musculus

<400> 77

Leu Leu Leu Trp Leu Thr Gly Ala Arg Cys Asp Ile Gln Met Thr Gln
 1 5 10 15

Ser Pro Ala Ser Leu Ser Ala Ser Val Gly Glu Thr Val Thr Ile Thr
 20 25 30

Cys Arg Ala Ser Gly Asn Ile His Asn Tyr Leu Thr Trp Tyr Gln Gln
 35 40 45

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

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

Tyr Ser Leu Lys Ile Asn Arg Leu Gln Pro Glu Asp Phe Gly Ser Tyr
 85 90 95

Tyr Cys Gln His Phe Trp Asn Ile Pro Trp Thr Phe Gly Gly Gly Thr
 100 105 110

Lys Leu Asn Ser Arg
 115

<210> 78
 <211> 114
 <212> PRT
 <213> Mus musculus

<400> 78

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

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

Lys Pro Glu Gln Gly Leu Glu Trp Ile Gly Tyr Ile Ser Pro Gly Asn

35

40

45

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

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

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

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

Ser Ser

<210> 79
 <211> 108
 <212> PRT
 <213> Mus musculus

<400> 79

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

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

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

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

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

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

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

<210> 80
 <211> 111
 <212> PRT
 <213> Mus musculus

<400> 80

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

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

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

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

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

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

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

<210> 81
 <211> 109
 <212> PRT
 <213> Mus musculus

<400> 81

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

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

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

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

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

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

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

<210> 82
<211> 109
<212> PRT
<213> Mus musculus

<400> 82

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

Ala Ser Gly Phe Ala Phe Ser Ser Tyr Asp Met Ser Trp Ile Arg Gln
20 25 30

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

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

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

Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg His Phe Tyr Arg Phe
85 90 95

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 83
<211> 113
<212> PRT
<213> Mus musculus

<400> 83

Leu Leu Leu Cys Val Ser Gly Ala Pro Gly Ser Ile Val Met Thr Gln

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

Ser

<210> 84
 <211> 112
 <212> PRT
 <213> Mus musculus

<400> 84

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

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Thr Gly Ala Trp Phe Ala Tyr Trp Ala Lys Asp Ser Ser Arg His
100 105 110

<210> 85
<211> 107
<212> PRT
<213> Mus musculus

<400> 85

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

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

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

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

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

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

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

<210> 86
<211> 118
<212> PRT
<213> Mus musculus

<400> 86

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

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

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

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

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

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

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

Val Thr Val Leu Leu Lys
115

<210> 87
<211> 109
<212> PRT
<213> Mus musculus

<400> 87

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

Glu Lys Val Thr Met His Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

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

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

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

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

<210> 88
 <211> 148
 <212> PRT
 <213> Mus musculus

<400> 88

Met Glu Trp Ser Gly Val Phe Ile Phe Leu Leu Ser Gly Thr Ala Gly
 1 5 10 15

Val Leu Ser Glu Val Gln Leu His Gln Phe Gly Ala Glu Leu Val Lys
 20 25 30

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

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

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

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

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

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

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

Pro Ser Val Tyr
 145

<210> 89
 <211> 139
 <212> PRT
 <213> Mus musculus

<400> 89

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

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

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

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

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

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

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

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

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

<210> 90
<211> 100
<212> PRT
<213> Mus musculus

<400> 90

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

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

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

Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu

50

55

60

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

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

Val Ser Ser Lys
100

<210> 91
<211> 90
<212> PRT
<213> Mus musculus

<400> 91

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

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

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

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

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

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

<210> 92
<211> 116
<212> PRT
<213> Mus musculus

<400> 92

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

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

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

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

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

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

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

Val Ser Ser Asn
115

<210> 93
<211> 100
<212> PRT
<213> Mus musculus

<400> 93

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

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

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

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

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

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

Ile Lys Gln Lys
100

<210> 94
<211> 108
<212> PRT
<213> Mus musculus

<400> 94

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

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

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

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

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

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

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

<210> 95
<211> 104
<212> PRT
<213> Mus musculus

<400> 95

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

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

Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser

35

40

45

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

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

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

Val Pro Ser Trp Arg Ser Asn Lys
 100

<210> 96
 <211> 109
 <212> PRT
 <213> Mus musculus

<400> 96

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

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

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

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

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

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

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

<210> 97
 <211> 94
 <212> PRT

<213> Mus musculus

<400> 97

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

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

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

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

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

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

<210> 98

<211> 111

<212> PRT

<213> Mus musculus

<400> 98

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

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

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

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

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

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

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

<210> 99
<211> 102
<212> PRT
<213> Mus musculus

<400> 99

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

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

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

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

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

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

Pro Ser Trp Lys Ser Asn
100

<210> 100
<211> 101
<212> PRT
<213> Mus musculus

<400> 100

Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Trp Met His
1 5 10 15

Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Met Ile
20 25 30

Asp Pro Ser Asn Ser Glu Thr Arg Leu Asn Gln Lys Phe Lys Asp Lys

35

40

45

Ala Thr Leu Asn Val Asp Lys Ser Ser Asn Thr Ala Tyr Met Gln Leu
50 55 60

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

Leu Arg His Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Thr Val
85 90 95

Thr Val Ser Ser Lys
100

<210> 101
<211> 99
<212> PRT
<213> Mus musculus

<400> 101

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

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

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

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

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

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

Ser Asn Lys

<210> 102
<211> 110
<212> PRT

<213> Mus musculus

<400> 102

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

Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met Ser Trp Val Arg Gln
20 25 30

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

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

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

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

Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
100 105 110

<210> 103

<211> 113

<212> PRT

<213> Mus musculus

<400> 103

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

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

Thr Ser Ile Asn Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

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

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

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

Tyr Leu Pro Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 104
<211> 111
<212> PRT
<213> Mus musculus

<400> 104

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

Val Ser Gly Phe Ser Leu Thr Thr Tyr Asp Leu His Trp Val Arg Gln
20 25 30

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

Ser Thr Asp Tyr Asn Ala Ala Phe Ile Ser Arg Leu Ser Ile Ser Lys
50 55 60

Asp Asn Ser Lys Ser Gln Val Phe Phe Lys Met Asn Ser Leu Gln Ala
65 70 75 80

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

Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
100 105 110

<210> 105
<211> 118
<212> PRT
<213> Mus musculus

<400> 105

Pro Ala Ser Ser Ser Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu

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

<210> 106
 <211> 114
 <212> PRT
 <213> Mus musculus

<400> 106

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

Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Arg Arg Ile Tyr Tyr Phe
85 90 95

Gly Arg Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
100 105 110

Ser Ser

<210> 107
<211> 118
<212> PRT
<213> Mus musculus

<400> 107

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

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

Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln
35 40 45

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

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

Phe Thr Leu Lys Ile Ser Arg Val Glu Pro Glu Asp Leu Gly Val Tyr
85 90 95

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

Ala Glu Ile Lys Leu Ala
115

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

<400> 108

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

Ala Ser Gly Phe Thr Phe Ser Asn Ser Trp Phe Asn Trp Val Arg Gln
20 25 30

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

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

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

Leu Arg Ala Glu Asp Thr Gly Ile Tyr Tyr Cys Thr Arg Pro Glu Thr
85 90 95

Ala Arg Ala Thr Phe Ala Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
100 105 110

Ser Ser

<210> 109

<211> 118

<212> PRT

<213> Mus musculus

<400> 109

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

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

Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln
35 40 45

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

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

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

Tyr Cys Phe Gln Gly Ser His Val Pro Arg Thr Phe Gly Gly Gly Thr
100 105 110

Lys Leu Asn Gln Thr Gly
115

<210> 110
<211> 111
<212> PRT
<213> Mus musculus

<400> 110

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

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

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

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

Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr
65 70 75 80

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

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

<210> 111
<211> 104
<212> PRT
<213> Mus musculus

<400> 111

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

Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr
20 25 30

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

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

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

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

Gly Thr Lys Leu Glu Ile Lys Gln
100

<210> 112
<211> 106
<212> PRT
<213> Mus musculus

<400> 112

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

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

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

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

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

Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly Thr Gly Asp Tyr Trp
- Page 153 -

85

90

95

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
100 105

<210> 113
<211> 112
<212> PRT
<213> Mus musculus

<400> 113

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

Val Ser Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
20 25 30

Leu Leu Asn Ser Arg Thr Arg Lys Asn Tyr Leu Ala Trp Val Gln His
35 40 45

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

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

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

Tyr Cys Arg Gln Ser Tyr Asn Leu Val Thr Phe Gly Ala Gly Pro Ser
100 105 110

<210> 114
<211> 112
<212> PRT
<213> Mus musculus

<400> 114

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

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

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

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

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

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

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

<210> 115
<211> 108
<212> PRT
<213> Mus musculus

<400> 115

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

Glu Thr Ile Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Tyr
20 25 30

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

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln His Asn Glu Tyr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 116
<211> 113

<212> PRT
<213> Mus musculus

<400> 116

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

Ala Ser Gly Tyr Ser Phe Thr Gly Tyr Phe Met Asn Trp Val Met Gln
20 25 30

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

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

Val Asp Lys Ser Ser Ser Thr Ala His Met Glu Leu Arg Ser Leu Ala
65 70 75 80

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

Tyr Gly Ser Ser Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Glu Pro His
100 105 110

His

<210> 117
<211> 108
<212> PRT
<213> Mus musculus

<400> 117

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

Glu Thr Ile Thr Ile Asn Cys Arg Ala Ser Lys Ser Ile Ser Lys Tyr
20 25 30

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

Tyr Ser Gly Ser Thr Leu Gln Ser Gly Ile Pro Ser Arg Phe Ser Gly

50

55

60

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

Glu Asp Phe Ala Met Tyr Tyr Cys Gln Gln His Asn Glu Tyr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 118
<211> 113
<212> PRT
<213> Mus musculus

<400> 118

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

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

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

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

Ala Asp Lys Ser Ser Ser Thr Val Tyr Met Glu Leu Ser Arg Leu Thr
65 70 75 80

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

Asp Tyr Asp Lys Ser Met Leu Trp Thr Thr Gly Val Lys Asn Leu Ile
100 105 110

Arg

<210> 119
<211> 108
<212> PRT

<213> Mus musculus

<400> 119

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

Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Ser Asn Gln Lys Asn Tyr
20 25 30

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 120

<211> 113

<212> PRT

<213> Mus musculus

<400> 120

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

Ala Ser Val Tyr Ala Phe Thr Asn Tyr Leu Ile Glu Trp Val Lys Gln
20 25 30

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

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

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

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

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

Pro

<210> 121
<211> 113
<212> PRT
<213> Mus musculus

<400> 121

Gln Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu
1 5 10 15

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

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

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

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

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

Ser Lys Leu Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 122
<211> 121
<212> PRT
<213> Homo sapiens

<400> 122

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser His
20 25 30

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

Gly Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys
50 55 60

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

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

Arg Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 123

<211> 112

<212> PRT

<213> Homo sapiens

<400> 123

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

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

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

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

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

Cys Glu Asp Phe Ala Ile Tyr Tyr Cys Leu Gly Glu Phe Ser Cys Gly
85 90 95

Ser Ala Asp Cys Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 124
<211> 121
<212> PRT
<213> Homo sapiens

<400> 124

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser His
20 25 30

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

Gly Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys
50 55 60

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

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

Arg Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 125
<211> 112
<212> PRT
<213> Homo sapiens

<400> 125

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

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

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

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

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

Cys Glu Asp Phe Ala Ile Tyr Tyr Cys Leu Gly Glu Phe Ser Cys Gly
85 90 95

Ser Ala Asp Cys Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 126

<211> 121

<212> PRT

<213> Homo sapiens

<400> 126

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser His
20 25 30

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

Gly Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys
50 55 60

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

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

Arg Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 127
<211> 113
<212> PRT
<213> Homo sapiens

<400> 127

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

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

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

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

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

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

Gly Ser Ala Asp Cys Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 128
<211> 121
<212> PRT
<213> Homo sapiens

<400> 128

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser His
20 25 30

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

Gly Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys
50 55 60

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

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

Arg Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 129
<211> 113
<212> PRT
<213> Homo sapiens

<400> 129

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

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

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

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

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Asn Leu

65					70					75					80
Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gly	Glu	Phe	Ser	Cys
				85					90					95	
Gly	Ser	Ala	Asp	Cys	Phe	Ala	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile
			100					105					110		

Lys

<210> 130
 <211> 121
 <212> PRT
 <213> Homo sapiens

<400> 130

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

<210> 131
 <211> 113
 <212> PRT

<213> Homo sapiens

<400> 131

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

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

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

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

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

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gly Glu Phe Ser Cys
85 90 95

Gly Ser Ala Asp Cys Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 132

<211> 121

<212> PRT

<213> Homo sapiens

<400> 132

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser His
20 25 30

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

Gly Asp Ile Arg Ser Gly Gly Ser Ala Tyr Tyr Ala Asn Trp Ala Lys
50 55 60

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

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

Arg Thr Asn Gly Pro Ser Asp Leu Thr Asn Arg Leu Asp Leu Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 133
<211> 113
<212> PRT
<213> Homo sapiens

<400> 133

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

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

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

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

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

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

Gly Ser Ala Asp Cys Phe Ala Phe Gly Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 134
<211> 5
<212> PRT
<213> Gallus gallus

<400> 134

Gly Tyr Asp Met Leu
1 5

<210> 135
<211> 17
<212> PRT
<213> Gallus gallus

<400> 135

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

Gly

<210> 136
<211> 19
<212> PRT
<213> Gallus gallus

<400> 136

Val Ala Gly Gly Cys Asn Ser Gly Tyr Cys Arg Asp Ser Pro Gly Ser
1 5 10 15

Ile Asp Ala

<210> 137
<211> 10
<212> PRT
<213> Gallus gallus

<400> 137

Ser Gly Gly Gly Ser Arg Asn Tyr Tyr Gly
1 5 10

<210> 138
<211> 7
<212> PRT
<213> Gallus gallus

<400> 138

Asp Asp Gln Arg Pro Ser Asn
1 5

<210> 139

<211> 11

<212> PRT

<213> Gallus gallus

<400> 139

Ser Ala Asp Ser Asn Thr Tyr Glu Gly Ser Phe
1 5 10

<210> 140

<211> 5

<212> PRT

<213> Mus musculus

<400> 140

Asp Tyr Asn Met Asp
1 5

<210> 141

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Ala Tyr Ser Met His
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Thr Gly Thr Asp Tyr Trp Gly Gln Gly Thr Thr
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Tyr Thr Ser Ser Leu Arg Ser
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Gln Gln Tyr Ser Lys Leu Pro Arg Thr
1 5

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Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His
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Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro
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Thr Asn Ala Met Asn

1 5

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Arg Ile Arg Ser Lys Ser Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val

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Asp Trp Asp Gly Phe Leu Tyr Phe Asp Tyr Trp
1 5 10

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

Ala Ser Gly Phe Thr Phe Asn Thr Asn Ala Met Asn Trp Val Arg Gln
20 25 30

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

Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr
50 55 60

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

Leu Lys Thr Glu Asp Thr Ala Met Tyr Tyr Cys Val Arg Asp Trp Asp

85

90

95

Gly Phe Leu Tyr Phe Asp Tyr Trp Ala Lys His His Leu Thr Leu Phe
 100 105 110

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Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln
 1 5 10 15

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 <212> PRT
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Leu Val Ser Asn Leu Glu Ser
 1 5

<210> 306
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Gln His Ile Arg Glu Leu Thr Arg Ser
 1 5

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

Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr
 20 25 30

Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro Arg Leu Leu Ile
 35 40 45

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

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

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Arg Glu Leu Thr Arg
85 90 95

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

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<400> 309

Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln Ala Ser
1 5 10