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(54) **Title:** PHARMACEUTICAL COMPOSITION FOR CANCER TREATMENT AND/OR PREVENTION

(54) 発明の名称： 癌の治療及び／又は予防用医薬組成物

(57) **Abstract:** The present invention provides: a conjugate obtained by linking an antibody, or a fragment thereof, that is immunologically responsive to CAPRIN-1 protein to an immune activation factor; and a pharmaceutical composition for cancer treatment and/or prevention which is characterized by including said conjugate as an effective component, and which has an antitumoral activity that is superior to conventional antibodies or conventional conjugates of antibodies and immune activation factors.

(57) 要約：本発明は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、免疫活性化因子が結合されてなるコンジュゲートならびに該コンジュゲートを有効成分として含むことを特徴とする、従来の抗体又は抗体と免疫活性化因子のコンジュゲートよりも抗腫瘍活性の優れた癌の治療及び／又は予防のための医薬組成物である。

WO 2018/079740 A1

Description

Title of Invention: PHARMACEUTICAL COMPOSITION FOR CANCER TREATMENT AND/OR PREVENTION

Technical Field

[0001]

The present invention relates to a conjugate of an antibody against a CAPRIN-1 protein and an immune activator, and medical use thereof as a therapeutic and/or preventive agent for a cancer, etc.

Background Art

[0002]

Various antibody drugs targeting specific antigenic proteins on cancer cells are applied as therapeutic drugs for cancers with fewer adverse reactions to cancer treatment because of their cancer specificity. For example, cytoplasmic-activation and proliferation-associated protein 1 (CAPRIN-1) is expressed on the cell membrane surface of many solid cancers, and antibodies against this CAPRIN-1 protein have been known to be promising in medical use for the treatment and/or prevention of cancers (Patent Literature 1).

[0003]

In recent years, studies have been made to enhance the pharmacological effects of the antibody drugs. Particularly, antibody-drug conjugates (ADCs) in which an antibody is conjugated with a drug having the strong ability to directly kill cells have been actively developed (Non Patent Literatures 1 and 2). As examples of ADCs, Kadcyla(R) (trastuzumab emtansine) comprising an existing antibody drug trastuzumab linked to a drug emtansine (DM1) which exhibits a cell-killing activity, and Adcetris(R) (brentuximab vedotin) comprising an anti-CD30 monoclonal antibody linked to monomethyl auristatin E (MMAE) are used in the treatment of some cancers. These ADCs have been found to prolong survival rates as compared with conventional treatment methods and found to be useful over existing methods

for treating cancers (Non Patent Literatures 3 and 4).

[0004]

In other cases, studies have also been made in an attempt to enhance pharmacological effects by conjugating immune activators to antibody drugs against cancers. For example, a conjugate of an existing antibody drug trastuzumab or cetuximab with resiquimod, one of the immune activators, or conjugates of an antibody drug rituximab against CD20 as a target antigen with various immune activators have been found to have an effect of enhancing the pharmacological effect of the antibody in animal models (Patent Literatures 2 and 3).

[0005]

As described above, attempts have been made to enhance the pharmacological effects of antibody drugs against cancers by conjugating various factors to various antibodies. However, antitumor effects strong enough to completely regress various cancers have not yet been obtained. Furthermore, effects of preventing cancer recurrence or metastasis, etc. have not been found.

Citation List

Patent Literature

[0006]

Patent Literature 1: WO2010/016526

Patent Literature 2: WO2014/012479

Patent Literature 3: U.S. Patent No. 8,951,528

Non Patent Literature

[0007]

Non Patent Literature 1: Lancet Oncol 2016; 17: e254-62

Non Patent Literature 2: Pharm Res. 2015 Nov; 32 (11): 3526-40

Non Patent Literature 3: New England Journal of Medicine 367; 19 (8), 2012, p. 1783-1791

Non Patent Literature 4: MAbs 2012; 4 (4): 458-65

Summary of Invention

Technical Problem

[0008]

An object of the present invention is to provide a solution to enhance the antitumor effect of an antibody or a fragment thereof against a CAPRIN-1 protein expressed on the cell membrane surface of cancer cells.

Solution to Problem

[0009]

The present inventor has conducted diligent studies and consequently completed the present invention by finding that: a conjugate of an antibody or a fragment thereof against a CAPRIN-1 protein and an immune activator exerts a much stronger antitumor effect than that of the antibody against the CAPRIN-1 protein or the fragment thereof used alone; and the effect of enhancing the antitumor effect by conjugating the antibody against the CAPRIN-1 protein or the fragment thereof to the immune activator is much superior to the effect of enhancing the antitumor effect by conjugating an existing antibody drug for a cancer to the immune activator.

[0010]

Specifically, the present invention has the following features (1) to (14):

(1) A conjugate of an antibody or a fragment thereof linked to an immune activator, wherein the antibody or the fragment thereof has immunological reactivity with a CAPRIN-1 protein having an amino acid sequence represented by any of even-numbered SEQ ID NOs among SEQ ID NOs: 2 to 30 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence.

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

(3) The conjugate according to (1) or (2), wherein the antibody is a monoclonal antibody or

a polyclonal antibody.

(4) The conjugate according to any of (1) to (3), wherein the antibody or the fragment thereof is any of the following (A) to (M):

(A) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(B) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(C) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(D) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(E) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(F) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(G) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(H) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(I) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(J) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(K) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(L) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 300, 301, and 302 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 304, 305, and 306 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein, and

(M) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein.

(5) The conjugate according to any of (1) to (4), wherein the antibody or the fragment thereof is any of the following (a) to (ak):

(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: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

(6) The conjugate according to any of (1) to (5), wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, or a single-chain antibody.

(7) The conjugate according to any of (1) to (6), wherein the immune activator is a ligand or an agonist binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR).

(8) The conjugate according to (7), wherein the Toll-like receptor (TLR) is TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, or TLR10.

(9) The conjugate according to (7) or (8), wherein the ligand or the agonist binding to the Toll-like receptor (TLR), or a derivative thereof is any of the following (i) to (vii):

(i) a TLR2-binding ligand or agonist selected from the group consisting of peptidoglycan, lipoprotein, lipopolysaccharide, and zymosan,

(ii) a TLR3-binding ligand or agonist selected from the group consisting of poly(I:C) and poly(A:U),

(iii) a TLR4-binding ligand or agonist selected from the group consisting of lipopolysaccharide (LPS), HSP60, RS09, and MPLA,

(iv) a TLR5-binding ligand or agonist selected from the group consisting of flagellin and FLA,

(v) a TLR7- or TLR8-binding ligand or agonist selected from the group consisting of an imidazoquinoline compound and single-stranded RNA,

(vi) a TLR9-binding ligand or agonist selected from the group consisting of bacterial DNA,

non-methylated CpG DNA, hemozoin, ODN1585, ODN1668, and ODN1826, and

(vii) a TLR10-binding ligand or agonist selected from the group consisting of profilin and a uropathogenic bacterium.

(10) The conjugate according to any of (1) to (9), wherein the antibody or the fragment thereof is linked to the immune activator via a linker.

(11) A pharmaceutical composition for the treatment and/or prevention of a cancer, comprising the conjugate according to any of (1) to (10) as an active ingredient.

(12) The pharmaceutical composition according to (11), wherein the cancer is a cancer expressing s CAPRIN-1 protein on the cell membrane surface.

(13) The pharmaceutical composition according to (11) or (12), wherein the cancer is a cancer selected from the group consisting of breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, and head and neck cancer.

(14) A method for treating and/or preventing a cancer, comprising administering the conjugate according to any of (1) to (10) or the pharmaceutical composition according to any of (11) to (13) to a subject.

Advantageous Effects of Invention

[0011]

The conjugate according to the present invention not only exerts a much stronger antitumor effect than that of an antibody against a CAPRIN-1 protein used alone but is superior in antitumor effect to a known conjugate of an antibody drug for a cancer and an immune activator. Also, the effect of enhancing the antitumor effect by the conjugate according to the present invention is superior to the effect of enhancing the antitumor effect by conjugating an existing antibody drug for a cancer to the immune activator. Thus, the conjugate according to the present invention is effective for the treatment or prevention of a

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cancer.

Description of Embodiments

[0012]

The conjugate of an antibody or a fragment thereof against a CAPRIN-1 protein (hereinafter, referred to as an "anti-CAPRIN-1 antibody") and an immune activator used in the present invention can be evaluated for its antitumor activity, as mentioned later, by examining *in vivo* the inhibition of tumor growth in a cancer-bearing animal.

[0013]

In the present invention, the "conjugate" refers to an antibody linked to an immune activator via a covalent bond. The linking between the antibody and the immune activator may be done by a linker.

[0014]

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

[0015]

The immune activator that is a constituent of the conjugate according to the present invention can be any factor activating immunocytes and is preferably a ligand or an agonist, or a derivative thereof, binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR), more preferably a ligand or an agonist, or a derivative thereof, binding to Toll-like receptor (TLR).

[0016]

The subject to be treated and/or prevented for cancer according to the present invention is a mammal such as a human, a pet animal, livestock, or a sport animal, and a preferred subject is a human.

[0017]

Hereinafter, the anti-CAPRIN-1 antibody, the immune activator, the conjugate of the anti-CAPRIN-1 antibody and the immune activator, the pharmaceutical composition comprising the conjugate, and the method for treating and/or preventing a cancer using the conjugate, according to the present invention will be described.

[0018]

<Anti-CAPRIN-1 antibody>

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

[0019]

The anti-CAPRIN-1 antibody used in the present invention may have immunological reactivity with a variant of the CAPRIN-1 protein having 80% or more, preferably 90% or more, more preferably 95% or more, further preferably 99% or more sequence identity to the amino acid sequence represented by any of even-numbered SEQ ID NOs among SEQ ID NOs: 2 to 30. In this context, the term "% sequence identity" means a percentage (%) of the number of identical amino acids (or bases) to the total number of amino acids (or bases) when two sequences are aligned so that the maximum degree of similarity can be achieved with or without introducing a gap.

[0020]

In the present invention, the anti-CAPRIN-1 antibody that is used for preparing the

conjugate means an antibody or a fragment thereof having immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof. In this context, the "immunological reactivity" means the property of the antibody binding to the CAPRIN-1 protein or a partial polypeptide thereof *in vivo*.

[0021]

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

[0022]

The polyclonal antibody having immunological reactivity with the full-length CAPRIN-1 protein or the fragment thereof (anti-CAPRIN-1 polyclonal antibody) can be obtained, for example, by immunizing a mouse, a human antibody-producing mouse, a rat, a rabbit, a chicken, or the like with a naturally occurring CAPRIN-1 protein, or a fusion protein thereof with GST or the like, or a partial peptide thereof and obtaining serum therefrom, and applying the obtained serum to ammonium sulfate precipitation, protein A, protein G, a DEAE ion-exchange column, an affinity column linked to a CAPRIN-1 protein or a partial peptide, or the like.

[0023]

As for the full-length CAPRIN-1 protein or the fragment thereof to be used in the immunization, the nucleotide sequences and amino acid sequences of CAPRIN-1 and homologs thereof are available, for example, by accessing GenBank (NCBI, USA) and using an algorithm such as BLAST or FASTA (Karlin and Altschul, Proc. Natl. Acad. Sci. USA, 90: 5873-5877, 1993; and Altschul et al., Nucleic Acids Res. 25: 3389-3402, 1997). Also, a method for preparing the CAPRIN-1 protein is available with reference to WO2014/012479, or can be carried out using, for example, cells expressing the CAPRIN-1 protein.

[0024]

The monoclonal antibody having immunological reactivity with the full-length CAPRIN-1 protein or the fragment thereof (anti-CAPRIN-1 monoclonal antibody) can be obtained, for example, by: administering SK-BR-3 (breast cancer cells expressing CAPRIN-1) or the full-length CAPRIN-1 protein or the fragment thereof, or the like to a mouse for

immunization; fusing spleen cells separated from the mouse with myeloma cells; and selecting a clone producing anti-CAPRIN-1 monoclonal antibodies from among the obtained fusion cells (hybridomas). The antibody produced from the hybridoma thus selected can be prepared in the same way as the method for purifying the polyclonal antibody mentioned above.

[0025]

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

[0026]

The human antibody can be obtained by: sensitizing EB virus-infected human lymphocytes, with the protein, protein-expressing cells, or lysates thereof; fusing the sensitized lymphocytes with human-derived myeloma cells such as U266 cells; and obtaining an antibody having immunological reactivity with the full-length CAPRIN-1 protein or the fragment thereof from the obtained fusion cells.

[0027]

The humanized antibody, also called reshaped human antibody, is an engineered antibody. The humanized antibody is constructed by grafting complementarity-determining regions of an antibody derived from an immunized animal onto complementarity-determining regions of a human antibody. A genetic engineering technique commonly used for constructing humanized antibodies is also well-known. Specifically, DNA sequences designed to link complementarity-determining regions of, for example, a mouse or rabbit antibody, to framework regions of a human antibody are synthesized by PCR from several prepared oligonucleotides having overlapping terminal portions. The obtained DNAs are ligated with DNAs encoding human antibody constant regions. The resulting ligation products are incorporated into expression vectors, which are then transferred to hosts for antibody production to obtain the antibody of interest. See, European Patent Application Publication No. EP239400 and International Publication No. WO96/02576). The framework regions of a human antibody connected via the complementarity-determining regions are selected so that the complementarity-determining regions form a favorable antigen-binding

site. If necessary, an amino acid in the framework regions of antibody variable regions may be substituted so that the complementarity-determining regions of a reshaped human antibody form an appropriate antigen-binding site (Sato K. et al., Cancer Research 1993, 53: 851-856). In addition, these framework regions may be replaced with framework regions derived from various human antibodies (see WO99/51743).

[0028]

Antibodies are typically heteromultimeric glycoproteins each comprising at least two heavy chains and two light chains. The antibodies are each composed of two identical light chains and two identical heavy chains. Each heavy chain has a heavy chain variable region at one end, followed by a series of constant regions. Each light chain has a light chain variable region at one end, followed by a series of constant regions. The variable regions contain certain variable regions called complementarity-determining regions (CDRs) and impart binding specificity to the antibody. Portions relatively conserved in the variable regions are called framework regions (FRs). The complete heavy chain and light chain variable regions each contain four FRs connected via three CDRs (CDR1 to CDR3).

[0029]

The sequences of human-derived heavy chain and light chain constant regions and variable regions are available from, for example, NCBI (USA; GenBank, UniGene, etc.). For example, the following sequences can be referred to: Accession No. J00228 for a human IgG1 heavy chain constant region; Accession No. J00230 for a human IgG2 heavy chain constant region; Accession Nos. V00557, X64135, X64133, etc., for a human light chain κ constant region; and Accession Nos. X64132, X64134, etc., for a human light chain λ constant region.

[0030]

A chimeric antibody is an antibody prepared from a combination of sequences derived from different animals and may be, for example, an antibody composed of heavy chain and light chain variable regions of a mouse antibody and constant regions of heavy chain and light chain variable regions of a human antibody. The chimeric antibody can be prepared using a method known in the art and is obtained, for example, by: ligating DNAs encoding the antibody V regions to DNAs encoding the human antibody C regions; incorporating the

resulting ligation products into expression vectors; and transferring the vectors into hosts for antibody production.

[0031]

The non-human animal antibody is obtained by immunizing an animal with a sensitizing antigen according to a method known in the art and, as a general method, by intraperitoneally, intracutaneously, or subcutaneously injecting a sensitizing antigen to an animal such as a mouse. For the injection of the sensitizing antigen, the antigen is mixed in an appropriate amount with various adjuvants including CFA (complete Freund's adjuvant), and the mixture is administered to the animal a plurality of times. The animal is immunized and then verified to contain anti-CAPRIN-1 antibodies in serum. The serum can be obtained and applied, as mentioned above, to ammonium sulfate precipitation, protein A, protein G, a DEAE ion-exchange column, an affinity column bound with a CAPRIN-1 protein or a partial peptide, or the like to obtain the non-human animal antibody. In the case of obtaining a monoclonal antibody from a non-human animal, immunocytes can be collected from an immunized animal and subjected to cell fusion with myeloma cells to obtain the monoclonal antibody. The cell fusion between the immunocytes and the myeloma cells can be carried out according to a method known in the art (see Kohler, G. and Milstein, C. Methods Enzymol. (1981) 73, 3-46).

[0032]

The antibody used in the present invention may be also obtained as a recombinant antibody produced using a genetic engineering technique by cloning genes of the antibody from a hybridoma; incorporating the antibody genes into appropriate vectors; and transferring the vectors into hosts (see Carl, A.K. Borrebaeck, James, W. Larrick, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990).

[0033]

The anti-CAPRIN-1 antibody that is used for obtaining the conjugate of the present invention may be an antibody in which an amino acid in a variable region (e.g., FR) or a constant region is substituted with another amino acid. The amino acid substitution is the

substitution of one or more, for example, less than 15, less than 10, 8 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less amino acids, preferably 1 to 9 amino acids. The substituted antibody should be an antibody that has the property of specifically binding to the antigen and binding affinity for the antigen equivalent to or greater than those of the corresponding unsubstituted antibody and causes no rejection when applied to humans.

[0034]

The anti-CAPRIN-1 antibody used in the present invention is expected to have a stronger antitumor effect, the higher binding affinity for the CAPRIN-1 protein on cancer cell surface the antibody has. Its association constant (affinity constant) Ka (kon/koff) is preferably at least 10^7 M^{-1}, at least 10^8 M^{-1}, at least 5 x 10^8 M^{-1}, at least 10^9 M^{-1}, at least 5 x 10^9 M^{-1}, at least 10^{10} M^{-1}, at least 5 x 10^{10} M^{-1}, at least 10^{11} M^{-1}, at least 5 x 10^{11} M^{-1}, at least 10^{12} M^{-1}, or at least 10^{13} M^{-1}.

[0035]

The binding activity of the anti-CAPRIN-1 antibody used in the present invention against effector cells can be improved by substituting one, two or several amino acids in the heavy chain constant region of the antibody or by removing fucose added to N-acetylglucosamine in a N-glycoside-linked sugar chain attached to the heavy chain constant region. Such an antibody may have the amino acid substitution alone or may be in a composition comprising a fucosylated antibody.

[0036]

The antibody in which one, two or several amino acids in the heavy chain constant region are substituted can be prepared with reference to, for example, WO2004/063351, WO2011/120135, U.S. Patent No. 8388955, WO2011/005481, U.S. Patent No. 6737056, and/or WO2005/063351.

[0037]

The antibody lacking fucose added to N-acetylglucosamine in a N-glycoside-linked sugar chain in the heavy chain constant region has been removed, or cells producing the antibody, can be prepared with reference to U.S. Patent No. 6602684, European Patent No. 1914244, and/or U.S. Patent No. 7579170. A composition of the antibody lacking fucose

added to N-acetylglucosamine in a N-glycoside-linked sugar chain attached to the heavy chain constant region, and the antibody having the fucose, or cells producing the composition can be prepared with reference to, for example, U.S. Patent No. 8642292.

[0038]

Methods for preparing and purifying the anti-CAPRIN-1 polyclonal antibody, the anti-CAPRIN-1 monoclonal antibody, and the antibody used in the present invention, and a method for preparing the CAPRIN-1 protein or the partial polypeptide thereof to be used in immunization can be carried out 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.

[0039]

Specific examples of the anti-CAPRIN-1 antibody according to the present invention include anti-CAPRIN-1 antibodies disclosed 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.

[0040]

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

[0041]

An antibody or a fragment thereof having immunological reactivity with a partial

polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 31 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the CAPRIN-1 protein; an antibody or a fragment thereof which comprises 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 has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0042]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID

NO: 33 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the CAPRIN-1 protein; or 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.

[0043]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 32 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0044]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 34 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0045]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 35 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the CAPRIN-1 protein; or an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0046]

An antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0047]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 296 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0048]

An antibody or a fragment thereof having immunological reactivity with a partial

polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 297 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0049]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 298 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0050]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 299 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid

sequence. Preferably, an antibody or a fragment thereof which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 300, 301, and 302 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 304, 305, and 306 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the 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: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

[0051]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 308 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0052]

An antibody or a fragment thereof having immunological reactivity with a partial polypeptide of the CAPRIN-1 protein having the amino acid sequence represented by SEQ ID NO: 309 or an amino acid sequence having 80% or more (preferably 85% or more, more preferably 90% or more, further preferably 95% or more) sequence identity to the amino acid sequence. Preferably, an antibody or a fragment thereof which comprises 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 has immunological reactivity with the 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.

[0053]

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

[0054]

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.

[0055]

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.

[0056]

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.

[0057]

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.

[0058]

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.

[0059]

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.

[0060]

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.

[0061]

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.

[0062]

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.

[0063]

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.

[0064]

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.

[0065]

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.

[0066]

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.

[0067]

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.

[0068]

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.

[0069]

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.

[0070]

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.

[0071]

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.

[0072]

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.

[0073]

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.

[0074]

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.

[0075]

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.

[0076]

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.

[0077]

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.

[0078]

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.

[0079]

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.

[0080]

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.

[0081]

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.

[0082]

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.

[0083]

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.

[0084]

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.

[0085]

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.

[0086]

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.

[0087]

An antibody or a fragment thereof comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

[0088]

In Examples mentioned later, conjugates with an immune activator were prepared using

the polyclonal antibody or the monoclonal antibody against the full-length CAPRIN-1 protein or a polypeptide of a partial region thereof expressed on the cell membrane surface of cancer cells, and verified to have a strong antitumor effect.

[0089]

<Immune activator>

Herein, the immune activator according to the present invention is a factor activating various immunocytes and means a naturally occurring compound, a nucleic acid, or a naturally occurring compound capable of maintaining or enhancing the immune functions of the cells. In this context, the "immunocytes" are T lymphocytes, B lymphocytes, NK cells, monocytes, dendritic cells, granulocytes, macrophages, myeloid-derived suppressor cells, Langerhans cells and precursor cell groups thereof, and these immunocyte groups present in tumor.

[0090]

Specific examples of the immune activator used in the present invention include, but are not particularly limited to, ligands or agonists binding to Toll-like receptor (TLR), NOD-like receptor (NLR), RIG-like receptor, or C-type lectin receptor (CLR).

[0091]

Specific examples of the ligand or the agonist binding to Toll-like receptor (TLR) include ligands or agonists binding to TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, or TLR10.

[0092]

Specific examples of the ligand or the agonist binding to TLR2 include substances selected from the group consisting of peptidoglycan, lipoprotein, lipopolysaccharide, and zymosan.

[0093]

Specific examples of the ligand or the agonist binding to TLR3 include substances selected from the group consisting of poly(I:C), poly(A:U) polyICLC (Hiltonol), and Ampligen.

[0094]

Specific examples of the ligand or the agonist binding to TLR4 include substances

selected from the group consisting of lipopolysaccharide (LPS), HSP60, RS09, MPLA (monophosphoryl lipid A from Salmonella minnesota R595), GLA-SE, G100, and MPLA.

[0095]

Specific examples of the ligand or the agonist binding to TLR5 include substances selected from the group consisting of flagellin and FLA.

[0096]

Specific examples of the ligand or the agonist binding to TLR7 or TLR8 include low-molecular compounds such as imidazoquinoline compounds, and single-stranded RNA. Specific examples thereof include Imiquimod, Resiquimod, Loxorbine, 852A, 854A, S-34240, Motolimod (VTX-2337), DSR-6434, GS-9620, ANA773, AZD8848/DSP-3025, GSK2245035, Gardiquimod, CL264, UC-1V150, CL075, CL097, CL307, CL347, 3M-003, 3M-0043, 3M-052, CL264, IV209, ORN R-2176-dT, Poly(dT), ORN R-0006, ORN R-0002, ORN R-2336, PolyU, ORN R-1886, polyG3, DSR6434, RWJ21757, SM324405, p-IMDQ, m-IMDQ and GSK2245035.

[0097]

Specific examples of the ligand or the agonist binding to TLR9 include substances selected from the group consisting of bacterial DNA, non-methylated CpG DNA, hemozoin, ODN1585, ODN1668, ODN1668, lefitolimod (MGN1703), SD-101, CYT003, CPG7909, DUK-CPG-001, and ODN1826.

[0098]

Specific examples of the ligand or the agonist binding to TLR10 include substances selected from the group consisting of profilin and uropathogenic bacteria.

[0099]

Among the ligands or the agonists binding to Toll-like receptor (TLR), the ligand or the agonist binding to TLR7 or TLR8 is preferably used in the present invention. A TLR7- or TLR8-binding ligand or agonist selected from the group consisting of imidazoquinoline compounds and single-stranded RNA is more preferably used as the ligand or the agonist binding to TLR7 or TLR8, and a TLR7- or TLR8-binding ligand or agonist selected from imidazoquinoline compounds is further preferably used.

[0100]

Preferred specific examples of the imidazoquinoline compound include compounds described in U.S. Patent No. 8,951,528 and compounds disclosed in WO2015/103989, for example, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinoline-4-amine (Imiquimod), 1-(4-amino-2-ethylaminomethylimidazo-[4,5-c]quinolin-1-yl)-2-methylpropan-2-ol (Gardiquimod), N-[4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl-]methanesulfonamide (PF-4878691), 4-amino-2-(ethoxymethyl)-a,a-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (Resiquimod), 4-amino-aa-dimethyl-2-methoxyethyl-1H-imidazo[4,5-c]quinoline-1-ethanol, 1-(2-(3-(benzyloxy)propoxy)ethyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, 4-amino-2-ethoxymethyl-aa-dimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol, N-(2-{2-[4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-n'-phenylurea, 1-2-amino-2-methylpropyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, 1-{4-[(3,5-dichlorophenyl)sulfonyl]butyl}-2-ethyl-1H-imidazo[4,5-c]quinolin-4-amine, N-(2-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-n'-cyclohexylurea, N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl}-n'-(3-cyanophenyl)thiourea, N-[3-(4-amino-2-butyl-1H-imidazo[4,5-c]quinolin-1-yl)-2,2-dimethylpropyl]benzamide, 2-butyl-1-[3-(methylsulfonyl)propyl]-1H-imidazo[4,5-c]quinolin-4-amine, though the imidazoquinoline compound is not limited thereto as long as the imidazoquinoline compound binds to TLR7 or TLR8.

[0101]

Specific examples of the ligand or the agonist binding to NOD-like receptor (NLR) include M-TriDAP and PGN. Other examples thereof include ligands or agonists against NOD1, for example, Tri-DAP, iE-DAP, and C12-iE. Further examples thereof include ligands or agonists against NOD2, for example, MDP, N-glycosyl-MDP, murabutide, M-TriLyS-D-ASN, M-TriLYS, and L18-MDP.

[0102]

Specific examples of the ligand or the agonist binding to RIG-like receptor include 5'ppp-dsRNA, poly(dA:dT), poly(dG:dC), and poly(I:C).

[0103]

Specific examples of the ligand or the agonist binding to C-type lectin receptor (CLR) include trehalose 6,6-dibehenate, zymosan, WGP, HKSC, HKCA, and curdlan AL.

[0104]

<Conjugate of anti-CAPRIN-1 antibody and immune activator>

In the present invention, the mode of binding between the anti-CAPRIN-1 antibody and the immune activator in the conjugate of the anti-CAPRIN-1 antibody and the immune activator is not particularly limited as long as it allows antitumor activity against a cancer to be maintained. The mode of binding preferably has a linker structure formed between the anti-CAPRIN-1 antibody and the immune activator.

[0105]

In this context, the linker means a compound capable of linking the anti-CAPRIN-1 antibody to the immune activator. Any of various linkers known in the art may be used, or an appropriate chemical modification to the structure of the activator may be used for directly binding the antibody to the activator.

[0106]

The details of the type of the linker and the binding method can be basically in accordance with a method known in the art (see, for example, Greg T. Hermanson Bioconjugate Techniques, Third Edition, WO2004010957, and WO2014/012479).

[0107]

In an embodiment of the present invention, examples of reactive groups attached to the anti-CAPRIN-1 antibody, the immune activator, and the linker include the following.

[0108]

Examples of the reactive group attached to the amino acid sequence of the antibody or a glycoprotein modifying an amino acid include primary amine (ε-amino group), carboxyl, thiol (sulfhydryl), carbonyl (ketone or aldehyde), and hydroxyl unless a special chemical modification is made. The primary amine exists at the N-terminus of a polypeptide or the side chain of a lysine residue and is positively charged under physiological conditions. The primary amine usually exists outside of the protein and can therefore be used in binding without denaturing the structure of the protein. The carboxyl exists at the C-terminus of a

polypeptide or the side chain of aspartic acid or glutamic acid. The sulfhydryl exists at the side chain of cysteine and forms a disulfide bond that maintains the higher-order structure of the protein. The ketone or aldehyde group is generated in a glycoprotein by the oxidation of glycosyl with sodium metaperiodate.

[0109]

The conjugate of the present invention is prepared by binding the linker to the reactive group of the antibody, binding thereto the immune activator bound with the linker, or directly binding the immune activator to the antibody.

[0110]

Examples of the reactive groups attached to the linker and the immune activator include the following.

[0111]

Reactive group capable of reacting with the amine: N-hydroxysuccinimide (NHS) ester, imide ester, pentafluorophenyl ester, hydroxymethyl phosphine, isothiocyanate, isocyanate, acyl azide, N-hydroxyl ester, sulfonyl chloride, aldehyde, glyoxal, epoxide, oxirane, carbonate, aryl, imide ester, carbodiimide, and carboxylic anhydride.

[0112]

Reactive group capable of reacting with the carboxyl and the amine: carbodiimide, diazoalkane, diazoacetyl compounds, and carbonyldiimidazole.

[0113]

Reactive group capable of reacting with the thiol: maleimide, haloacetamide, pyridyl disulfide, thiosulfone, vinyl sulfone, haloacetyl, aziridine, acryloyl, and aryl.

[0114]

Reactive group capable of reacting with the aldehyde: hydrazide and alkoxyamine. Reactive group capable of reacting with the hydroxyl: epoxy, oxirane, carbonyldiimidazole, N,N'-disuccinimidyl carbonate, N-hydroxysuccinimidyl chloroformate, and isocyanate.

[0115]

Reactive group capable of reacting with the hydroxyl: isocyanate.

[0116]

Photoreactive reactive group: diaziridine, aryl azide, aryl, benzophenol, and diazo compounds.

[0117]

Specific examples of the linker having the reactive group include the following.

[0118]

As a linker having the same reactive group ends, a linker having N-hydroxysuccinimide ester as a reactive group (e.g., Disuccinimidyl Glutarate (DSG), disuccinimidyl suberate (DSS), bis(sulfosuccinimidyl)suberate (BS3), tris-(succinimidyl)aminotriacetate (TSAT), PEGylated bis(sulfosuccinimidyl)suberate ($BS(PEG)_5$, $BS(PEG)_9$), dithiobis (succinimidyl propionate) (DSP), (DTSSP), (EGS), (Sulfo-EGS), (DMA), (DMP), (DMS), (DTBP), (DFDNB), (DST), (BSOCOES), (EGS), (Sulfo-EGS)) and a linker having maleimide as a reactive group (e.g., (BMOE), (BMB), (BMH), (TMEA), (BM(PEG)2), ($BM(PEG)_3$), (DTME), and (DMDB)).

[0119]

As a linker having different reactive group ends, a linker having NHS ester and maleimide as reactive groups (e.g., AMAS, BMPS, GMBS, Sulfo-MBS, MBS, Sulfo-MBS, SMCC, Sulfo-SMCC, EMCS, Sulfo-EMCS, SMPB, Sulfo-SMPB, SMPH, LC-SMCC, Sulfo-KMUS, $SM(PEG)_2$, $SM(PEG)_4$, $SM(PEG)_6$, $SM(PEG)_8$, $SM(PEG)_{12}$, and $SM(PEG)_{24}$), a linker having NHS ester and pyridyldithiol as reactive groups (e.g., SPDP, LC-SPDP, Sulfo-LC-SPDP, SMPT, PEG4-SPDP, and PEG12-SPDP), a linker having NHS ester and haloacetyl as reactive groups (e.g., SIA, SBAP, SIAB, and Sulfo-SIAB), a linker having NHS ester and aryl azide as reactive groups (e.g., ANB-NOS, Sulfo-SANPAH, and ATFB), a linker having NHS ester and diaziridine as reactive groups (e.g., SDA, Sulfo-SDA, LC-SDA, SDAD, and Sulfo-SDAD), a linker having carbodiimide as reactive groups (e.g., DCC, EDC, EDAC, NHS, and Sulfo-NHS), a linker having maleimide and hydrazide as reactive groups (e.g., BMPH, EMCH, MPBH, and KMUH), a linker having pyridyldithiol and hydrazide as a reactive group (e.g., PDPH), a linker having isocyanate and maleimide as reactive groups (e.g., PMPI), and a linker having NHS ester and psoralen as reactive groups (e.g., SPB).

[0120]

As other linkers, a linker containing a polypeptide, for example, Fmoc-Ala-Ala-Asn-

PAB, Fmoc-Ala-Ala-Asn(Trt)-PAB, Fmoc-PEG_3-Ala-Ala-Asn(Trt)-PAB, Fmoc-PEG_4-Ala-Ala-Asn(Trt)-PAB, Fmoc-Ala-Ala-Asn-PAB-PNP, Fmoc-Ala-Ala-Asn(Trt)-PAB-PNP, Fmoc-PEG_3-Ala-Ala-Asn(Trt)-PAB-PNP, Azide-PEG_4-Ala-Ala-Asn(Trt)-PAB-PNP, Mal-PEG_4-Ala-Ala-Asn(Trt)-PAB-PNP, Fmoc-Val-Cit-PAB-OH, Val-Cit-PAB-OH, Fmoc-Val-Cit-PAB-PNP, MC-Val-Cit-PAB, MC-Val-Cit-PAB-PNP.

[0121]

Also, Bis-PEG-acid, PEG Acid (e.g., Acid-PEG-TEMPO, Amino-PEG-acid, Amino-PEG-CH_2CO_2H, Aminoxy-PEG-acid, Azido-PEG-acid, Carboxy-PEG-sulfonic acid, Fmoc-N-amido-PEG-acid, Fmoc-N-amido-PEG-CH_2CO_2H, Fmoc-aminooxy-PEG-acid, Hydroxy-PEG-acid, Hydroxy-PEG-CH_2CO_2H, m-PEG-acid, m-PEG-$(CH_2)_3$-acid, Methoxytrityl-N-PEG-acid, N-methyl-N-(t-Boc)-PEG-acid, Propargyl-PEG-acid, Propargyl-PEG-CH_2CO_2H, Propargyl-PEG-$(CH_2)_3$-acid, t-Boc-N-amido-PEG-acid, t-Boc-N-amido-PEG-CH_2CO_2H, t-Boc-Aminooxy-PEG-acid, Acid-PEG-PFP ester, Miscellaneous PEG acid), PEG PFP ester (e.g., Acid-PEG-PFP ester, Bis-PEG-PFP ester), Bis-PEG-NHS, PEG Aldehyde (e.g., m-PEG-aldehyde, m-PEG-benzaldehyde, Ald-PEG-acid, Ald-PEG-amine, Ald-PEG-azide, Ald-PEG-NH-Boc, Ald-PEG-NHS ester, Ald-PEG-TFP ester, Ald-PEG-t-butyl ester), PEG Tosylate (e.g., Azido-PEG-Tos, Hydroxy-PEG-Tos, m-PEG-Tos, t-Boc-Aminooxy-PEG-Tos, Trifluoroethyl-PEG-Tos, Tos-PEG-acid, Tos-PEG-CH_2CO_2H, Tos-PEG-alkyne, Tos-PEG-t-butyl ester, Tos-PEG-CH_2CO_2tBu, Tos-PEG-Tos, S-acetyl-PEG6-Tos, N-Tos-N-(t-butoxycarbonyl)-aminooxy-PEG_4-Tos, Ms-PEG-Ms, Ms-PEG-t-butyl ester, PEG-Ms, Propargyl-PEG-Ms), Boc-PEG (e.g., Amino-PEG-t-Boc-Hydrazide, Azido-PEG-t-Boc-Hydrazide, Boc-NH-PEG-NH-Boc, Bromoacetamido-PEG-Boc-amine, m-PEG-ONHBoc, Mal-Alkyl-t-Boc-amine, N-Boc-PEG-alcohol, N-Boc-PEG-bromide, N-methyl-N-(t-Boc)-PEG-acid, t-Boc-N-amido-PEG-acid, t-Boc-N-amido-PEG-CH_2CO_2H, t-Boc-N-Amido-PEG-amine, t-Boc-N-amido-PEG-azide, t-Boc-N-amido-PEG-NHS ester, t-Boc-N-amido-PEG-sulfonic acid), PEG NHS ester (e.g., Acid-PEG-NHS ester, Azido-PEG-NHS ester, Bis-PEG-NHS, Fmoc-PEG-NHS ester, m-PEG-NHS ester, m-PEG-NHS Carbonate, Mal-PEG-NHS ester, Propargyl-PEG-NHS ester, t-Boc-N-amido-PEG-NHS ester, t-Butoxycarbonyl-PEG-NHS ester), Fmoc-PEG (e.g., Fmoc-N-amido-PEG-acid, Fmoc-NH-PEG-CH_2CO_2H, Fmoc-

PEG-NHS ester), Biotin PEG (e.g., Biotin PEG-acid, Biotin PEG-alcohol, Biotin PEG-alkyne, Biotin PEG-amine, Biotin PEG-azide, Biotin PEG-DBCO, Biotin PEG-hydrazide, Biotin-PEG-Mal, Biotin-PEG-NHS, Biotin-EDA-PEG-NHS, Biotin-PEG-oxyamine, Biotin-PEG-PFP, Biotin-EDA-PEG-PFP, Biotin-PEG-Tetrazine, Biotin-PEG-TFP, Azide-SS-biotin, Biotin-PEG3-SS-azide, DBCO-S-S-PEG3-Biotin, Dde Biotin-PEG4-Alkyne, Dde Biotin-PEG_4-Azide, Dde Biotin-PEG_4-DBCO, Diazo Biotin-PEG_3-Alkyne, Diazo Biotin-PEG_3-Azide, Diazo Biotin-PEG3-DBCO, Diol Biotin-PEG_3-Alkyne, Diol Biotin-PEG_3-Azide, PC Biotin-PEG_3-Alkyne, PC-Biotin-PEG_4-PEG_4-Alkyne, PC-Biotin-PEG_4-PEG4-Alkyne, PC Biotin-PEG_3-Azide, PC-Biotin-PEG4-PEG3-Azide, PC-Biotin-PEG_4-NHS carbonate, PC DBCO-PEG_3-Biotin, WSPC Biotin-PEG_3-DBCO, Fmoc-Lys (biotin-PEG)-OH, Fmoc-N-amido-(PEG-biotin)-acid, TAMRA-Azide-PEG-Biotin), PEG Phosphonate, Aminooxy PEG (e.g., Aminooxy-PEG-acid, Aminooxy-PEG-alcohol, Aminooxy-PEG-azide, Aminooxy-PEG-bromide, Aminooxy-PEG-methane, Aminooxy-PEG-Propargyl, Aminooxy-PEG-t-butyl ester, Aminooxy-PEG-Thiol, Bis-(Aminooxy)-PEG, t-Boc-Aminooxy-PEG-acid, t-Boc-Aminooxy-PEG-alcohol, t-Boc-Aminooxy-PEG-amine, t-Boc-Aminooxy-PEG-Azide, t-Boc-Aminooxy-PEG-Bromide, t-Boc-aminooxy-PEG-Methane, t-Boc-aminooxy-PEG-Propargyl, t-Boc-aminooxy-PEG-S-Ac, t-Boc-Aminooxy-PEG-Thiol, t-Boc-Aminooxy-PEG-Tos, Fmoc-aminooxy-PEG-acid, Trifluoroethyl-PEG-Aminooxy), Alkyne PEG (e.g., endo-BCN-PEG, exo-BCN-PEG, Propargyl-PEG-acid, Propargyl-PEG-CH_2CO_2H, Propargyl-PEG-$(CH_2)_3$-acid, Propargyl-PEG-$(CH_2)_3$-methyl ester, Propargyl-PEG-Acrylate, Propargyl-PEG-alcohol, Propargyl-PEG-amine, Propargyl-PEG-methylamine, Aminooxy-PEG-Propargyl, Propargyl-PEG-azide, Propargyl-PEG-bromide, Propargyl-PEG-Maleimide, Propargyl-PEG-Ms, Propargyl-PEG-NHS ester, Propargyl-PEG-sulfonic acid, Propargyl-PEG-t-butyl ester, Propargyl-PEG-CH_2CO_2tBu, Propargyl-PEG-thiol, Propargyl-PEG-5-nitrophenyl carbonate, t-Boc-aminooxy-PEG-Propargyl, Bis-Propargyl-PEG, m-PEG-Propargyl), Azido PEG (e.g., Azido-PEG-acid, Azido-PEG-CH_2CO_2H, Azido-PEG-$(CH_2)_3$-methyl ester, Azido-PEG-Acrylate, Azido-PEG-alcohol, Azido-PEG-$(CH_2)_3OH$, Azido-PEG-amine, Azido-PEG-azide, Azido-PEG-Maleimide, Azido-PEG-methylamine, Azido-PEG-methyl ester, Azido-PEG-NHS ester, Azido-PEG-CH_2CO_2-NHS, Azido-PEG-oxazolidin-2-one, Azido-PEG-PFP ester,

Azido-PEG-phosphonic acid, Azido-PEG-phosphonic acid ethyl ester, Azido-PEG-sulfonic acid, Azido-PEG-t-Boc-Hydrazide, Azido-PEG-t-butyl ester, Azido-PEG-CH_2CO_2-t-butyl ester, Azido-PEG-TFP ester, Azido-PEG-Tos, Aminooxy-PEG-azide, Bromo-PEG-azide, Bromoacetamido-PEG-azide, Carboxyrhodamine 110-PEG-Azide, Isothiocyanato-PEG-Azide, Isothiocyanato-PEG-Azide, m-PEG-azide, Propargyl-PEG-azide, TAMRA-PEG-Azide, t-Boc-N-Amido-PEG-Azide, t-Boc-Aminooxy-PEG-Azide, Thiol-PEG-Azide, Trifluoroethyl-PEG-Azide, Azido-PEG-amino acid, Azido-PEG_4-4-nitrophenyl carbonate, S-Acetyl-PEG_3-Azido, Azide, Trityl-PEG_{10}-Azide), Alkyne PEG, DBCO-PEG, BCN-PEG, Propargyl-PEG, Bis-PEG-acid, Bis-PEG-NHS, Bis-PEG-PFP, Bis-Propargyl-PEG, Amine-PEG-Amine, Azido-PEG-azide, Bromo-PEG, or Mal PEG may be used.

[0122]

The linker between the anti-CAPRIN-1 antibody and the immune activator may be composed of a single linker or composed of a plurality of linkers.

[0123]

A method for preparing the conjugate of the anti-CAPRIN-1 antibody and the immune activator according to the present invention includes a method which involves binding the immune activator using a ε-amino group at the lysine side chain of the antibody, and a method which involves binding the immune activator using thiol formed by the reduction treatment of a cysteine residue constituting the disulfide bond of the antibody.

[0124]

In the case of using a ε-amino group at the lysine residue of the antibody, for example, a method is used which involves reacting active ester (e.g., N-hydroxysuccinimide ester) therewith to form an amide bond. In this case, since the antibody contains many lysine residues, the binding reaction proceeds nonspecifically.

[0125]

In the case of using thiol constituting a disulfide bond present at the cysteine side chain of the antibody, a method is used which involves forming thiol from the disulfide bond on the antibody using a reducing agent such as mercaptoethanol, and reacting the thiol with maleimide or α-haloamide. For example, a method using sulfone phenyloxadiazole, a 4-

cyanoethynyloxy derivative, or the like is used for stabilizing a thiol-mediated bond. These bonds are stable for a longer time than the bond based on the conjugate addition reaction of cysteine with maleimide. Also, a linker having an amino group near an imide group can be used because an imide ring with a thiol group added to maleimide is opened by hydrolysis so that stability is improved owing to the resulting amide bond. In the antibody, the thiols of cysteines form a disulfide bond. Thus, an alternative method involves binding the immune activator, etc. to between two thiols via the thiols. As an example, a cross-linked bond may be formed using a linker having two disulfide bond sites that can be formed from an amide group having two sulfones at the β position, or dibromomaleimide.

[0126]

The conjugate of the present invention can be obtained by a method using, for example, the THIOMAB™ technique, which is a method capable of introducing a determined number of thiol groups at a particular site of an antibody (see Nature Biotechnology 26, 925-932 (2008)).

[0127]

The conjugate of the present invention can be formed, for example, by reducing the antibody using a reducing agent dithiothreitol (DTT) in a phosphate buffer to obtain an antibody having a reactive thiol group, which is then conjugated with the immune activator. The conjugate can be obtained by adding a thiol group to primary amine at the lysine residue of the antibody by the introduction of a Traut's reagent (2-iminothiolane or N-succinimidyl S-acetylthioacetate (SATA)), instead of the method using a reducing agent.

[0128]

The amount of the thiol added to the antibody can be determined, for example, by mixing a sample solution containing 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB) and an SH group with a phosphate buffer solution (pH 8.0) and distilled water, adding a solution of DTNB dissolved in a phosphate buffer, a Good's buffer, or a Tris bufferto the mixture, and incubating the resulting mixture for a given time, followed by the measurement of absorbance at 412 nm (see G.L. Ellman, Arch. Biochem. Biophys., 82, 70 (1959)).

[0129]

The thiol group added by the cleavage of the disulfide bond of the antibody through reduction treatment is preferably treated (capped) in order to prevent the formation of a disulfide bond again. The capping can employ, for example, N-ethylmaleimide (NEM) or 2-iodoacetamide (IAA).

[0130]

The conjugate through can be constructed binding the immune activator to the antibody using the thiol group added to the antibody according to a method known in the art. Specifically, the binding can be carried out using, for example, a linker reagent having a maleimide group or a bromoacetamide group as a linker reagent specifically binding to the thiol group of the reduced antibody. For example, N-succinimidyl-4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (SMCC) is used as the linker having a maleimide group. In this case, the N-succinimide group of SMCC can form an amide bond with an amino group present in the immune activator to obtain the conjugate.

[0131]

In another embodiment, an amide bond is first formed at an amino group present in the activator using SMCC. Then, the maleimide group of the SMCC bound with the immune activator can be reacted with the thiol group added to the antibody to obtain the conjugate.

[0132]

In an alternative embodiment, the conjugate of the antibody and the immune activator may be formed using two linkers. For example, a primary amino group present at the lysine residue of the antibody is bound to the N-succinimide group of SATA (N-succinimidyl-S-acetylthioacetate) via an amide bond to add a thiol group to the antibody. SMCC is reacted with the immune activator containing an amino group or with the immune activator having an amino group added thereto according to an ordinary method to form an amide bond with the N-succinimide group of the SMCC. The maleimide group of the SMCC bound with the immune activator can be reacted with the thiol group of the SATA bound with the antibody to obtain the conjugate.

[0133]

In a further alternative embodiment, examples of the preparation of the conjugate of the

antibody and the immune activator include a method using maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-Val-Cit-PAB) as a linker. MC-val-Cit-PAB is a linker cleavable by intracellular protease (e.g., cathepsin B). A thiol group is added to the antibody dissolved in a phosphate bufferusing DTT or the like. Meanwhile, the immune activator having an amino group is reacted with the benzyloxycarbonyl (PAB) in MC-Val-Cit-PAB to prepare an immune activator bound with MC-val-Cit-PAB, which can then be reacted with the thiol-added antibody mentioned above to obtain the conjugate.

[0134]

In a further alternative embodiment, SATA is bound to a primary amino group at the lysine residue of the antibody to add a thiol group thereto. Meanwhile, succinimidyl 3-(2-pyridyldithio)propionate (SPDP) is reacted with the immune activator having an amino group to form an amide bond with the N-succinimide group of the SPDP. In order to obtain a composition comprising the antibody bound with the linker, for example, a peak fraction of a higher molecular weight as compared with the antibody before the binding of the linker can be separated by the application of gel filtration chromatography or the like.

[0135]

The number of molecules of the bound immune activator per antibody molecule in the conjugate of the anti-CAPRIN-1 antibody and the immune activator of the present invention can be characterized using a method such as mass spectrometry, ELISA, electrophoresis, or HPLC based on a method known in the art.

[0136]

<Antitumor effect of conjugate>

The conjugate of the anti-CAPRIN-1 antibody and the immune activator of the present invention has cytotoxic activity *in vitro* or *in vivo*. Accordingly, the antitumor effect of the conjugate of the present invention may be determined by examining its cytotoxic activity against a cancer. The cytotoxic activity can be evaluated by: administering the conjugate to an organism having a cancer; and examining the size of the tumor over time via measuring the size of the tumor after the administration. The antitumor effect of the present invention can also be evaluated by examining a survival rate. Alternatively, the antitumor effect of the

present invention may be evaluated by examining the ability to produce a cytokine or a chemokine. The antitumor effect of the conjugate of the present invention can be further determined by examining the prevention of a cancer, the prevention of metastasis, or the prevention of recurrence.

[0137]

The conjugate of the present invention is expected to have a stronger antitumor effect, the higher binding affinity for the CAPRIN-1 protein on cancer cell surface the conjugate has. Its association constant (affinity constant) Ka (kon/koff) is preferably at least 10^7 M^{-1}, at least 10^8 M^{-1}, at least 5 x 10^8 M^{-1}, at least 10^9 M^{-1}, at least 5 x 10^9 M^{-1}, at least 10^{10} M^{-1}, at least 5 x 10^{10} M^{-1}, at least 10^{11} M^{-1}, at least 5 x 10^{11} M^{-1}, at least 10^{12} M^{-1}, or at least 10^{13} M^{-1}.

[0138]

The ability of the conjugate of the present invention to bind to CAPRIN-1 can be identified through the use of binding assay using, for example, ELISA, Western blot, immunofluorescence, or flow cytometry.

[0139]

The conjugate of the present invention enhances the antitumor effect as compared with the anti-CAPRIN-1 antibody alone, as mentioned above. The rate of the enhancement 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, furthermore preferably 65% or more, most preferably 70% or more. The rate of enhancement in antitumor effect by the conjugate of the present invention with respect to 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 10 days or later after the start of the administration.

[0140]

<Pharmaceutical composition and method for treating and/or preventing cancer>

The target of the pharmaceutical composition for the treatment and/or prevention of a cancer of the present invention is not particularly limited as long as the target is cancer (cells) expressing the CAPRIN-1 protein.

[0141]

The terms "tumor" and "cancer" used in the present specification mean malignant neoplasm and are used interchangeably with each other.

[0142]

The cancer targeted in the present invention may be any cancer expressing the CAPRIN-1 protein on the cell membrane surface. The cancer is preferably breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, or head and neck cancer as mentioned above.

[0143]

More specifically, examples of these cancers include, but are not limited to, breast adenocarcinoma, complex-type breast adenocarcinoma, malignant mixed tumor of the mammary gland, intraductal papillary adenocarcinoma, lung adenocarcinoma, squamous cell cancer, small-cell cancer, large-cell cancer, glioma which is tumor of neuroepithelial tissue, glioblastoma, neuroblastoma, ependymoma, neuronal tumor, embryonal neuroectodermal tumor, neurilemmoma, neurofibroma, meningioma, chronic lymphocytic leukemia, lymphoma, gastrointestinal lymphoma, alimentary lymphoma, small to medium cell-type lymphoma, cecal cancer, ascending colon cancer, descending colon cancer, transverse colon cancer, sigmoid colon cancer, rectal cancer, epithelial ovarian cancer, germ cell tumor, stromal cell tumor, pancreatic ductal carcinoma, invasive pancreatic ductal carcinoma, pancreatic adenocarcinoma, acinar cell carcinoma, adenosquamous carcinoma, giant cell tumor, intraductal papillary-mucinous neoplasm, mucinous cystic neoplasm, pancreatoblastoma, islet-cell adenoma, Frants tumor, serous cystadenocarcinoma, solid-pseudopapillary tumor, gastrinoma, glucagonoma, insulinoma, multiple endocrine neoplasia type-1 (Wermer's syndrome), nonfunctional islet cell tumor, somatostatinoma, VIPoma, uterine cervix cancer, uterine body cancer, fibrosarcoma, sarcoma of bones or joints, Ewing's sarcoma, Wilms tumor, hepatoblastoma, soft tissue sarcoma, acute leukemia, chronic leukemia, spinal cord tumor, malignant soft tissue tumor,

teratoma group tumor, and head and neck cancer including hypopharynx cancer, oropharynx cancer, tongue cancer, epipharynx cancer, oral cancer, lip cancer, sinus cancer, and throat cancer.

[0144]

The subjects (patients) to be targeted are preferably mammals, for example, mammals including primates, pet animals, livestock, and sport animals and are particularly preferably humans, dogs, and cats.

[0145]

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

[0146]

An aseptic composition for injection can be formulated according to conventional pharmaceutical practice using a vehicle such as injectable distilled water. Examples of aqueous solutions for injection include physiological saline, isotonic solutions containing glucose and other auxiliary agents, for example, D-sorbitol, D-mannose, D-mannitol, and sodium chloride. These solutions may be used in combination with an appropriate solubilizer, for example, an alcohol (specifically, ethanol) or a polyalcohol (e.g., propylene glycol and polyethylene glycol), or a nonionic surfactant, for example, Polysorbate 80™ or HCO-60. Examples of oil solutions include sesame oil and soybean oil. These solutions may be used in combination with benzyl benzoate or benzyl alcohol as a solubilizer. The solutions may be

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

[0147]

The administration is carried out orally or parenterally, preferably parenterally. Specific examples of its dosage forms include injections, intranasal administration preparations, transpulmonary administration preparations, and percutaneous administration preparations. Examples of the injections include intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, and intratumoral administration, through which the pharmaceutical composition can be administered systemically or locally.

[0148]

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

[0149]

The pharmaceutical composition for the treatment and/or prevention of a cancer comprising the conjugate of the present invention as an active ingredient can be administered to a subject to treat and/or prevent the aforementioned cancer expressing CAPRIN-1 on the

cell membrane surface, preferably breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, or head and neck cancer.

Examples

[0150]

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

[0151]

Example 1 Anti-CAPRIN-1 polyclonal antibody

In order to obtain anti-CAPRIN-1 polyclonal antibodies having immunological reactivity with the CAPRIN-1 protein to be used in conjugates, 1 mg of a recombinant human CAPRIN-1 protein of SEQ ID NO: 2 or SEQ ID NO: 4 produced according to Example 3 of WO2010/016526 was mixed with an equal volume of incomplete Freund's adjuvant (IFA) solution, and this mixture was subcutaneously administered to rabbits four times every 2 weeks. Then, blood was collected to obtain antiserum containing polyclonal antibodies. The obtained antiserum was purified using a (GE Healthcare Bio-Sciences Corp.) to prepare a polyclonal antibody against the CAPRIN-1 protein (anti-CAPRIN-1 polyclonal antibody #1). Also, the serum of a rabbit obtained without administering an antigen was purified using a protein G carrier in the same way as above and used as a rabbit control antibody.

[0152]

The following polyclonal antibodies #2 to #6 against partial polypeptides of CAPRIN-1 were obtained in the same way as in the method for preparing the polyclonal antibody against the CAPRIN-1 protein.

[0153]

Anti-CAPRIN-1 polyclonal antibody #2 against a partial CAPRIN-1 polypeptide represented by SEQ ID NO: 37 disclosed in WO2011/096528 (SEQ ID NO: 31 of the present specification), anti-CAPRIN-1 polyclonal antibody #3 against a partial polypeptide represented by SEQ ID NO: 5 disclosed in WO2013/018894 (SEQ ID NO: 32 of the present specification), anti-CAPRIN-1 polyclonal antibody #4 against a partial polypeptide represented by SEQ ID NO: 5 disclosed in WO2013/125654 (SEQ ID NO: 33 of the present specification), anti-CAPRIN-1 polyclonal antibody #5 against a partial polypeptide represented by SEQ ID NO: 37 disclosed in WO2011/096533 (SEQ ID NO: 34 of the present specification), and anti-CAPRIN-1 polyclonal antibody #6 against a partial polypeptide represented by SEQ ID NO: 37 disclosed in WO2011/096534 (SEQ ID NO: 35 of the present specification).

[0154]

Example 2 Anti-CAPRIN-1 monoclonal antibody

The following anti-CAPRIN-1 monoclonal antibodies were used in the conjugate of the present invention.

[0155]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 39 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 43 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0156]

The monoclonal antibody against CAPRIN-1 disclosed in WO2015/020212, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46,

respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 47 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 51 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0157]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096519, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 55 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 59 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0158]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125654, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively (e.g., an antibody comprising the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 63 comprising the CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 67 comprising the CDR1, CDR2, and CDR3 of light chain variable region).

[0159]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096517, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented

by the amino acid sequence of SEQ ID NO: 68 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69.

[0160]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79.

[0161]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096533, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 80 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 81, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 82 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 83.

[0162]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096534, wherein

the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 84 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 85, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 86 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 87.

[0163]

The monoclonal antibody against CAPRIN-1 disclosed in WO2010/016526, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 88 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 89; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 90 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 91; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 92 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 93; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 94 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 95; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 96 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 97; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 98 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 99; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 100 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 101.

[0164]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018894, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 102 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 103, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 104 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 105.

[0165]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018892, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 107.

[0166]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018891, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 108 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 109.

[0167]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018889, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 110 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 111.

[0168]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018883, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 112 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 113.

[0169]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125636, wherein

the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 114 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 115.

[0170]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125654, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 116 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 117, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 118 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 119.

[0171]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125630, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 120 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 121.

[0172]

The monoclonal antibody against CAPRIN-1 disclosed in WO2015/020212, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 122 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 123; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 124 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 125; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 128 and the amino acid sequence of a light chain variable region represented

by the amino acid sequence of SEQ ID NO: 129; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133.

[0173]

A nucleotide sequence was designed to express a heavy chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, which are from one of the above-mentioned anti-CAPRIN-1 monoclonal antibodies, and framework region sequences of a human antibody. The nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1. Similarly, a nucleotide sequence was designed to express a light chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, and framework region sequences of a human antibody; and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a light chain constant region of human IgG1. These two recombinant expression vectors were transferred to mammalian cells according to a conventional method, and a culture supernatant containing humanized monoclonal antibody #1 (humanized antibody #1) against CAPRIN-1 comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, was obtained from the cells.

[0174]

Similarly, a nucleotide sequence was designed to express a heavy chain variable region represented by SEQ ID NO: 47 comprising CDR1, CDR2, and CDR3 consisting of the amino

acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and framework region sequences of a human antibody; and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1. Similarly, a nucleotide sequence was designed to express a light chain variable region represented by SEQ ID NO: 51 comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively, and framework region sequences of a human antibody; and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1. These two recombinant expression vectors were transferred to mammalian cells according to a conventional method, and a culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #2 (humanized antibody #2) comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively, was obtained from the cells.

[0175]

A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #3 (humanized antibody #3) comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, was prepared in a similar way.

[0176]

A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #4 (humanized antibody #4) comprising CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively,

was prepared in a similar way.

[0177]

Culture supernatants containing the following humanized anti-CAPRIN-1 monoclonal antibodies #9 to #41 (humanized antibodies #9 to #41) were prepared in a similar way.

[0178]

Humanized monoclonal antibody #9 (humanized antibody #9) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69.

[0179]

Humanized monoclonal antibody #10 (humanized antibody #10) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71.

[0180]

Humanized monoclonal antibody #11 (humanized antibody #11) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73.

[0181]

Humanized monoclonal antibody #12 (humanized antibody #12) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75.

[0182]

Humanized monoclonal antibody #13 (humanized antibody #13) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77.

[0183]

Humanized monoclonal antibody #14 (humanized antibody #14) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79.

[0184]

Humanized monoclonal antibody #15 (humanized antibody #15) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 80 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 81.

[0185]

Humanized monoclonal antibody #16 (humanized antibody #16) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 82 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 83.

[0186]

Humanized monoclonal antibody #17 (humanized antibody #17) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 84 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 85.

[0187]

Humanized monoclonal antibody #18 (humanized antibody #18) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 86 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 87.

[0188]

Humanized monoclonal antibody #19 (humanized antibody #19) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 88 and the amino acid sequence of a light chain variable region represented by

the amino acid sequence of SEQ ID NO: 89.

[0189]

Humanized monoclonal antibody #20 (humanized antibody #20) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 90 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 91.

[0190]

Humanized monoclonal antibody #21 (humanized antibody #21) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 92 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 93.

[0191]

Humanized monoclonal antibody #22 (humanized antibody #22) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 94 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 95.

[0192]

Humanized monoclonal antibody #23 (humanized antibody #23) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 96 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 97.

[0193]

Humanized monoclonal antibody #24 (humanized antibody #24) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 98 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 99.

[0194]

Humanized monoclonal antibody #25 (humanized antibody #25) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of

SEQ ID NO: 100 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 101.

[0195]

Humanized monoclonal antibody #26 (humanized antibody #26) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 102 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 103.

[0196]

Humanized monoclonal antibody #27 (humanized antibody #27) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 104 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 105.

[0197]

Humanized monoclonal antibody #28 (humanized antibody #28) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 107.

[0198]

Humanized monoclonal antibody #29 (humanized antibody #29) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 108 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 109.

[0199]

Humanized monoclonal antibody #30 (humanized antibody #30) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 110 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 111.

[0200]

Humanized monoclonal antibody #31 (humanized antibody #31) comprising the amino

acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 112 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 113.

[0201]

Humanized monoclonal antibody #32 (humanized antibody #32) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 114 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 115.

[0202]

Humanized monoclonal antibody #33 (humanized antibody #33) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 116 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 117.

[0203]

Humanized monoclonal antibody #34 (humanized antibody #34) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 118 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 119.

[0204]

Humanized monoclonal antibody #35 (humanized antibody #35) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 120 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 121.

[0205]

Humanized monoclonal antibody #36 (humanized antibody #36) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 122 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 123.

[0206]

Humanized monoclonal antibody #37 (humanized antibody #37) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 124 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 125.

[0207]

Humanized monoclonal antibody #38 (humanized antibody #38) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127.

[0208]

Humanized monoclonal antibody #39 (humanized antibody #39) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 128 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 129.

[0209]

Humanized monoclonal antibody #40 (humanized antibody #40) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131.

[0210]

Humanized monoclonal antibody #41 (humanized antibody #41) comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133.

[0211]

On the basis of humanized antibody #1 among these anti-CAPRIN-1 monoclonal antibodies, a nucleotide sequence was designed to express a heavy chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and framework region sequences of a

human antibody. This nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a heavy chain constant region of human IgG1 in which serine (Ser) at amino acid position 239 in EU numbering is substituted with aspartic acid (Asp), and isoleucine (Ile) at amino acid position 332 in EU numbering is substituted with glutamic acid (Glu). Also, a nucleotide sequence was designed to express the amino acid sequence of a light chain variable region comprising CDR1, CDR2, and CDR3 consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, and framework region sequences of a human antibody, and the nucleotide sequence was inserted into a mammalian expression vector with an insert encoding a light chain constant region of human IgG1. These two recombinant expression vectors were transferred to mammalian cells according to a conventional method; and a culture supernatant containing humanized monoclonal antibody #5 (humanized antibody #5) against CAPRIN-1 composed of the full-length heavy chain amino acid sequence consisting of the heavy chain variable region designed above and the heavy chain constant region of human IgG1 in which serine (Ser) at amino acid position 239 in EU numbering is substituted with aspartic acid (Asp), and isoleucine (Ile) at amino acid position 332 in EU numbering is substituted with glutamic acid (Glu), and the full-length light chain amino acid sequence consisting of the light chain variable region designed above and the human light chain constant region, was obtained from the cells.

[0212]

A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #6 (humanized antibody #6) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of the humanized antibody #2 produced above was prepared in a similar way.

[0213]

A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #7 (humanized antibody #7) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of the humanized antibody #3 produced above was prepared in a similar way.

[0214]

A culture supernatant containing humanized anti-CAPRIN-1 monoclonal antibody #8 (humanized antibody #8) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of the humanized antibody #4 produced above was prepared in a similar way.

[0215]

Culture supernatants containing each of humanized anti-CAPRIN-1 antibodies #42 to #74 (humanized antibodies #42 to #74) comprising the amino acid sequence of the heavy chain variable region and the amino acid sequence of the light chain variable region of each of the humanized antibodies #9 to #41 produced above were prepared in a similar way.

[0216]

The obtained culture supernatants containing each of the humanized anti-CAPRIN-1 monoclonal antibodies #1 to #74 were subjected to purification using Hitrap Protein A Sepharose FF (GE Healthcare) according to a conventional method. The buffer was replaced with PBS(-). The resultant was filtered through a 0.22 μm filter (Merck Millipore Corp.) to prepare the humanized antibodies.

[0217]

Example 3 Preparation of conjugate of anti-CAPRIN-1 antibody and immune activator

Conjugates of anti-CAPRIN-1 polyclonal antibodies #1 to #6 described in Example 1 with resiquimod, an immune activator, were prepared using maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-val-Cit-PAB-PNP) as a linker. The preparation of these conjugates was carried out with reference to the method described in WO2014/012479.

[0218]

20 mg/mL of anti-CAPRIN-1 polyclonal antibody #0 described in Example 1 dissolved in PBS(-) was subjected to buffer replacement with a solution of 500 mM sodium borate and 500 mM sodium chloride (pH 8.0). After incubation of the antibody solution at 37°C for 30 minutes with 100 mM dithiothreitol (DTT), the buffer was replaced with a PBS(-) solution containing 1 mM diethylenetriaminepentaacetic acid (DTPA) using Sephadex G25, and the resultant was cooled on ice to prepare "reduced" anti-CAPRIN-1 polyclonal antibody #0.

[0219]

The amount of thiol per antibody molecule (thiol/antibody ratio) was determined by reacting the antibody with DTNB and measuring the absorbance at 412 nm and the absorbance at 280 nm.

[0220]

Resiquimod (Enzo Life Sciences, Inc.) and MC-Val-Cit-PABC-PNP (Medchem Express) were mixed in DMSO to allow the amino group of resiquimod to react with the benzyloxycarbonyl of MC-Val-Cit-PABC-PNP, thereby preparing a MC-val-Cit-PAB-bound resiquimod solution, which was then added to the reduced anti-CAPRIN-1 polyclonal antibody #1 prepared above for reaction thereof. After the reaction, an excess amount of maleimide was added to terminate the reaction, thereby preparing a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #1 described in Example 1 with resiquimod. The obtained conjugate was concentrated by ultrafiltration and desalted using Sephadex G25 into a PBS(-) solution. The resultant was sterilized by filtration through a 0.22 μm filter to prepare a solution containing the conjugate of anti-CAPRIN-1 polyclonal antibody #1 and resiquimod (Conjugate 1).

[0221]

A solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #2 and resiquimod (Conjugate 2), a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #3 and resiquimod (Conjugate 3), a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #4 and resiquimod (Conjugate 4), a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #5 and resiquimod (Conjugate 5), and a solution of a conjugate of anti-CAPRIN-1 polyclonal antibody #6 and resiquimod (Conjugate 6) were prepared in the same way as described above.

[0222]

As for the rabbit control antibody described in Example 1 unreactive with the CAPRIN-1 protein, a solution containing a conjugate of the rabbit control antibody and resiquimod (Control conjugate 1) was also prepared in the same way as described above.

[0223]

A solution containing a conjugate of humanized antibody #1, which is an anti-

CAPRIN-1 monoclonal antibody described in Example 2, with the immune activator resiquimod (Conjugate 7) was prepared using the humanized antibody #1 in the same way as above.

[0224]

A solution containing a conjugate of humanized antibody #2, which is an anti-CAPRIN-1 antibody described in Example 2, with the immune activator resiquimod (Conjugate 8) was prepared using the humanized antibody #2 in the same way.

[0225]

A solution containing a conjugate of humanized antibody #3 described in Example 2 with the immune activator resiquimod (Conjugate 9); a solution containing a conjugate of humanized antibody #4 with the immune activator resiquimod (Conjugate 10); a solution containing a conjugate of humanized antibody #5 with the immune activator resiquimod (Conjugate 11); a solution containing a conjugate of humanized antibody #6 with the immune activator resiquimod (Conjugate 12); a solution containing a conjugate of humanized antibody #7 with the immune activator resiquimod (Conjugate 13); a solution containing a conjugate of humanized antibody #8 with the immune activator resiquimod (Conjugate 14); and solutions containing conjugates of humanized antibodies #9 to #74 with the immune activator resiquimod (Conjugates 45 to 110), were each prepared as described above.

[0226]

The prepared solutions containing Conjugates 1 to 14, Conjugates 45 to 110, and Control conjugate 1 were each filtered through a 0.22 μm filter (Merck Millipore Corp.) to prepare the conjugates.

[0227]

Example 4 Preparation of conjugate of anti-CAPRIN-1 antibody and immune activator

Conjugates of the anti-CAPRIN-1 polyclonal antibodies described in Example 1 with an immune activator were prepared by the following method. 1-(2(2-aminoethoxy)-2-methylpropyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, a resiquimod derivative made by two-carbon homologation of the tertiary hydroxy group of resiquimod and the addition of an amino group thereto, was prepared as an immune activator by synthesis

according to an ordinary method.

[0228]

Specifically, dry acetonitrile, triethylamine, and trityl chloride were added to resiquimod, and reacted in an argon atmosphere. After the reaction, the residue was purified by silica gel column chromatography. The purified product was dissolved in dehydrated DMF and reacted with added 3-Boc-1,2,3-oxathiazolidine 2,2-dioxide. The aqueous phase was subjected to extraction with ethyl acetate according to an ordinary method. The obtained organic phase was then purified by column chromatography to prepare the above-mentioned resiquimod derivative.

[0229]

Next, the following procedure was carried out with reference to the method described in J. Med. Chem., (2008) 51, 6916-6926 in order to bind the obtained resiquimod derivative to succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC), as a linker.

[0230]

The resiquimod derivative was dissolved in dehydrated dichloromethane in an argon atmosphere. To the solution, diisopropylethylamine and SMCC were added. The mixture was allowed to react at room temperature for 2 hours. The reaction mixture was subjected to purification to obtain a condensate of resiquimod with SMCC.

[0231]

A conjugate of the condensate of resiquimod with the linker SMCC and anti-CAPRIN-1 antibody was prepared according to an ordinary method with reference to the methods described in U.S. Patent No. 8,951,528 and JIMD Reports-Case and Research Reports, 2012/5.

[0232]

Specifically, to anti-CAPRIN-1 polyclonal antibody #1 dissolved in a phosphate buffer, N-succinimidyl S-acetylthioacetate (SATA) (Thermo Fischer Scientific, Inc.) dissolved in a 10-fold molar mass of DMSO relative to the antibody was added, and reacted at room temperature for 30 minutes at pH 8. Then, the buffer was replaced with a phosphate buffer containing 10 mM EDTA using a desalting column (Thermo Fischer Scientific, Inc.) to obtain a solution containing anti-CAPRIN-1 polyclonal antibody #1 bound with SATA. To the

solution, a phosphate buffer containing 0.5 M hydroxylamine and 25 mM EDTA was added in a volume of 10% relative to the solution, and the mixture was deacetylated through reaction at room temperature for 2 hours. The buffer in the solution containing anti-CAPRIN-1 polyclonal antibody #1 bound with deacetylated SATA was replaced with a phosphate buffer using a desalting column as described above to prepare a solution containing a thiol group-added anti-CAPRIN-1 antibody.

[0233]

The condensate prepared above, dissolved in a 10- to 50-fold molar mass of DMSO relative to such antibody, was added to the solution and the mixture was reacted at room temperature for 1 hour. After the reaction, the buffer was replaced with a PBS(-) solution using a desalting column, and the resultant was concentrated using an ultrafiltration column and sterilized by filtration through a 0.2 μm filter to obtain a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #1 described in Example 1 with the resiquimod derivative (Conjugate 15).

[0234]

In the same way as above, a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #2 with the resiquimod derivative (Conjugate 16), a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #3 with the immune activator (Conjugate 17), a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #4 with the immune activator (Conjugate 18), a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #5 with the immune activator (Conjugate 19), and a solution containing a conjugate of anti-CAPRIN-1 polyclonal antibody #6 with the immune activator (Conjugate 20) were prepared.

[0235]

As for the rabbit control antibody described in Example 1 unreactive with the CAPRIN-1 protein, a solution containing a conjugate (Control conjugate 2) was also prepared in the same way as above using the rabbit control antibody.

[0236]

A solution containing a conjugate of humanized antibody #1, which is one of the anti-

CAPRIN-1 monoclonal antibodies described in Example 2, with the resiquimod derivative (Conjugate 21) was prepared in the same way as above.

[0237]

A solution containing a conjugate of humanized antibody #2, which is one of the anti-CAPRIN-1 antibodies described in Example 2, with the resiquimod derivative (Conjugate 22) was obtained in the same way.

[0238]

In the same way as above, a solution containing a conjugate of humanized antibody #3, which is an anti-CAPRIN-1 antibody described in Example 2, with the immune activator (Conjugate 23); a solution containing a conjugate of humanized antibody #4 with the immune activator (Conjugate 24); a solution containing a conjugate of humanized antibody #5 with the immune activator (Conjugate 25); a solution containing a conjugate of humanized antibody #6 with the immune activator (Conjugate 26); a solution containing a conjugate of humanized antibody #7 with the immune activator (Conjugate 27); and a solution containing a conjugate of humanized antibody #8 with the immune activator (Conjugate 28) were prepared.

[0239]

In the same way as above, solutions containing conjugates of humanized antibodies #9 to #74 with the immune activator (Conjugates 111 to 176) were each prepared.

[0240]

The prepared solutions containing Conjugates 15 to 28, Conjugates 111 to 176, and Control conjugate 2 were each filtered through a 0.22 μm filter (Merck Millipore Corp.) to prepare the conjugates.

[0241]

Example 5 Specific reactivity of conjugate with CAPRIN-1 protein and CAPRIN-1-expressing cancer cell

Conjugates 1 to 14 and Conjugates 45 to 110 prepared in Example 3 and Conjugates 15 to 28 and Conjugates 111 to 176 prepared in Example 4 were assayed for their specific reactivity with a CAPRIN-1 protein and their reactivity with the cell membrane surface of human cancer cells and mouse cancer cells which expressing a CAPRIN-1 protein.

[0242]

The specific reactivity with the CAPRIN-1 protein was determined by ELISA. A 1 μg/mL CAPRIN-1 protein solution was added at 100 μL/well to a 96-well plate, and the plate was left to stand at 4°C for 18 hours. Each well was washed with PBS-T three times. Then, a 0.5% bovine serum albumin (BSA) solution was added at 400 μL/well, and the plate was left to stand at room temperature for 3 hours. The solution was removed, and the wells were washed with 400 μL/well of PBS-T three times. Then, each of the solutions containing Conjugates 1 to 6, Conjugates 15 to 20, Control conjugate 1, and Control conjugate 2 was added at 100 μL/well, and the plate was left to stand at room temperature for 2 hours. Each well was washed with PBS-T three times. Then, an HRP-labeled anti-rabbit antibody diluted 5000-fold with PBS was added at 100 μL/well, and left to stand at room temperature for 1 hour. Each well was washed with PBS-T three times. Then, a TMB substrate solution was added at 100 μL/well, and left to stand for 15 to 30 minutes for chromogenic reaction. After the color development, the reaction was terminated by the addition of 1 N sulfuric acid at 100 μL/well, and the absorbance values at 450 nm and 595 nm were measured using an absorption spectrometer. As a result, Conjugates 1 to 6 and Conjugates 15 to 20 exhibited a higher absorbance value than that of Control conjugates 1 and 2 as negative controls and were found to specifically react with the CAPRIN-1 protein.

[0243]

Next, the reactivity with the cell membrane surface of CAPRIN-1-expressing cancer cells was verified by flow cytometry. Human breast cancer cells BT-474 (from ATCC) or mouse breast cancer cells 4T1 (from ATCC) were centrifuged in 1.5 mL microcentrifuge tubes (2×10^5 cells per tube). 100 μL of the solutions containing each of Conjugates 1 to 6, Conjugates 15 to 20, Control conjugate 1, and Control conjugate 2 was then each added to separate tubes. The tube was left to stand on ice for 1 hour. After washing with PBS, Alexa 488-labeled anti-rabbit IgG (H + L) diluted 100-fold with PBS(-) containing 0.5% FBS (0.5% FBS-PBS(-)) was added thereto, and the tube was left to stand on ice for 1 hour. After washing with 0.5% FBS-PBS(-), the cells were suspended in 0.2 μg/mL propidium iodide and 0.5% FBS-PBS(-), and the fluorescence intensity was measured using FACSVerse™ (Becton,

Dickinson and Company). As a result, Conjugates 1 to 6 and Conjugates 15 to 20, which were the conjugates of the anti-CAPRIN-1 polyclonal antibodies and the immune activator, were found to exhibit higher fluorescence intensity than that of Control conjugate 1 and Control conjugate 2 as negative controls, i.e., to strongly react with the cell surface of the human cancer cells BT474 and the mouse cancer cells 4T1 expressing CAPRIN-1.

[0244]

The reactivity of the conjugates with the following various human cancer cells and mouse cancer cells was verified in a similar way: breast cancer cells (BT-474), colorectal cancer cells (HT-29), lung cancer cells (QG56 and H1650), stomach cancer cells (NCI-N87), uterine cancer cells (HEC-1-A), prostate cancer cells (22Rv1), pancreatic cancer cells (Panc10.5), liver cancer cells (Hep3B), ovary cancer cells (SKOV3), kidney cancer cells (Caki-2), brain tumor cells (U-87MG), bladder cancer cells (T24), esophagus 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 found to express the CAPRIN-1 gene; and mouse kidney cancer cells (Renca) and mouse breast cancer cells (4T1), which are mouse cancer cells found to express the CAPRIN-1 gene. As a result of the verification, Conjugates 1 to 6 and Conjugates 15 to 20, which were the conjugates of the anti-CAPRIN-1 antibodies and the immune activator, exhibited stronger fluorescence intensities for all of the cancer cells than that of Control conjugate 1 and Control conjugate 2 as negative controls and were thus shown to strongly react with the cell membrane surface of the above cancer cells expressing CAPRIN-1.

[0245]

Also, anti-CAPRIN-1 polyclonal antibodies #1 to #6 prepared in Example 1 which are unconjugated with the immune activator were similarly assayed. As a result of assaying their reactivity with the above cancer cells expressing CAPRIN-1 by flow cytometry, these antibodies exhibited fluorescence intensities equivalent to those of Conjugates 1 to 6 and Conjugates 15 to 20.

[0246]

Next, Conjugates 7 to 14 and Conjugates 45 to 110, which were the conjugates of the

anti-CAPRIN-1 monoclonal antibodies with the immune activator prepared in Example 3, and Conjugates 21 to 28 and Conjugates 111 to 176 prepared in Example 4 were assayed for their specific reactivity with the CAPRIN-1 protein and their reactivity with the cell membrane surface of human cancer cells and mouse cancer cells expressing CAPRIN-1, in the same way as above. As a result, Conjugates 7 to 14 and Conjugates 21 to 28 exhibited significantly higher absorbance values than a negative control with PBS(-) added and were therefore shown to specifically react with the CAPRN-1 protein.

[0247]

Conjugates 7 to 14, Conjugates 45 to 110, Conjugates 21 to 28, and Conjugates 111 to 176 were further evaluated for their reactivity with the cell membrane surface of cancer cells expressing the CAPRIN-1 protein. As a result, these conjugates exhibited significantly stronger reactivity than that of a conjugate of the immune activator and human IgG unreactive with the CAPRIN-1 protein, and also exhibited strong reactivity equivalent to that of anti-CAPRIN-1 monoclonal antibodies #1 to #74 described in Example 2 which are unconjugated with the immune activator.

[0248]

These results demonstrated that the conjugates of the anti-CAPRIN-1 antibodies and the immune activator prepared above (Conjugates 7 to 14, Conjugates 45 to 110, Conjugates 21 to 28, and Conjugates 111 to 176) specifically bind to the CAPRIN-1 protein and to the cell membrane surface of CAPRIN-1-expressing cancer cells.

[0249]

Example 6 Antitumor effect of conjugate - 1

Next, Conjugates 1 to 6 and Conjugates 15 to 20 prepared using anti-CAPRIN-1 polyclonal antibodies #1 to #6 and Conjugates 7 to 14 and Conjugates 21 to 28 prepared using anti-CAPRIN-1 monoclonal antibodies in Examples 3 and 4 were evaluated for their *in vivo* antitumor effects on cancer-bearing mice.

[0250]

Specifically, the conjugates of the present invention were examined for their antitumor effect using NOD-SCID mice in which human-derived cancer cells expressing the CAPRIN-1

protein were transplanted. Human breast cancer cells BT474 were mixed with Matrigel (Sigma-Aldrich Corp.) and subcutaneously transplanted at 10^7 cells/mouse to the mice, which were then grown until tumor became 180 mm^3 or larger to prepare cancer-bearing mice. BT474 expresses the CAPRIN-1 protein on the cell membrane surface. As shown in Example 5, Conjugates 1 to 6 and Conjugates 15 to 20 prepared using anti-CAPRIN-1 polyclonal antibodies #1 to #6, and Conjugates 7 to 14 and Conjugates 21 to 28 prepared using anti-CAPRIN-1 monoclonal antibodies specifically bind to the cell membrane surface. Conjugates 1 to 28 were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice.

[0251]

A solution containing a conjugate of trastuzumab and resiquimod was prepared by the method described in Example 3 and administered as a comparative control in the same amount as above to the cancer-bearing mice. BT474 expresses HER2 protein, which is a target antigen of trastuzumab, on the cell membrane surface. The conjugate of trastuzumab and resiquimod specifically binds to BT474. The administration to the cancer-bearing mice was carried out once a week.

[0252]

PBS(-) was administered to the cancer-bearing mice, for a negative control.

[0253]

The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor) x (Length of the minor axis of tumor)^2 x 0.5. As a result of the evaluation, all the mice given Conjugates 1 to 6 prepared in Example 3 and Conjugates 15 to 20 prepared in Example 4 had less than 37% tumor volumes 50 days after the start of the administration relative to the tumor volume of the negative control (100%). All the mice given Conjugates 7 to 14 and Conjugates 21 to 28 had less than 15% tumor volumes. Cancer growth in the mice given Conjugates 11 to 14 and Conjugates 25 to 28 was suppressed early as compared with cancers in the mice given Conjugates 7 to 10 and Conjugates 21 to 24. As a result of similarly evaluating the *in vivo* antitumor effects of

Conjugates 45 to 176 on cancer-bearing mice, all the mice had less than 20% tumor volumes.

[0254]

On the other hand, the tumor volume of the mice given the solution containing the conjugate of trastuzumab and resiquimod as a comparative control was 54% relative to the negative control.

[0255]

These evaluation results demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 prepared in Examples 3 and 4 using the antibodies against CAPRIN-1 exert a significantly stronger antitumor effect than that of the negative control. These results also demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 have a significantly stronger antitumor effect than that of the conjugate of trastuzumab and resiquimod prepared as a comparative control.

[0256]

Example 7 Antitumor effect of conjugate - 2

The conjugates of the anti-CAPRIN-1 antibodies and the immune activator (Conjugates 1 to 28) prepared in Examples 3 and 4 were evaluated for their *in vivo* antitumor effects on cancer-bearing mice.

[0257]

Specifically, the conjugates of the present invention were examined for their antitumor effect using Balb/c nude mice in which human-derived cancer cells expressing CAPRIN-1 were transplanted. Human lung cancer cells H1650 were subcutaneously transplanted to the ventral regions of the mice, which were then grown until tumor became 180 mm^3 or larger to prepare cancer-bearing mice. The lung cancer cells H1650 express the CAPRIN-1 protein on the cell membrane surface. As shown in Example 5, Conjugates 1 to 28 specifically bind to CAPRIN-1 on the cell membrane surface of the lung cancer cells H1650. Conjugates 1 to 14 prepared in Example 3 and Conjugates 15 to 28 prepared in Example 4 were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice.

[0258]

A solution containing a conjugate of cetuximab and resiquimod was prepared by the method described in Example 3 and administered as a comparative control in the same amount

as above to the cancer-bearing mice. The administration was carried out once a week a total of three times.

[0259]

PBS(-) was administered to the cancer-bearing mice, for a negative control.

[0260]

The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor) x (Length of the minor axis of tumor)^2 x 0.5. As a result, the mice given Conjugates 1 to 6 and Conjugates 15 to 20 had less than 22% tumor volumes 25 days after the start of the administration relative to the tumor volume of the negative control (100%). All the mice given Conjugates 7 to 14 and Conjugates 21 to 28 had less than 12% tumor volumes. Cancer growth in the mice given Conjugates 11 to 14 and Conjugates 25 to 28 was suppressed early as compared with cancers in the mice given Conjugates 7 to 10 and Conjugates 21 to 24. As a result of similarly evaluating the *in vivo* antitumor effects of Conjugates 45 to 176 on cancer-bearing mice, the mice had less than 16% tumor volumes.

[0261]

On the other hand, the tumor volume of the mice given the solution containing the conjugate of cetuximab and resiquimod as a comparative control was 32% relative to the negative control.

[0262]

These evaluation results demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 exert a significantly stronger antitumor effect than that of the negative control. These results also demonstrated that Conjugates 1 to 28 and Conjugates 45 to 176 have a significantly stronger antitumor effect than that of the conjugate of cetuximab and resiquimod as a comparative control.

[0263]

Example 8 Preparation of conjugate of mouse chimeric anti-CAPRIN-1 monoclonal antibody and immune activator

Mouse chimeric antibodies composed of a heavy chain comprising the heavy chain variable region of each anti-CAPRIN-1 monoclonal antibody and the heavy chain constant region of mouse IgG, and a light chain comprising the light chain variable region of the anti-CAPRIN-1 monoclonal antibody and the light chain constant region of mouse IgG were prepared, and then conjugates of the antibodies with the immune activator resiquimod were prepared in the same way as in Example 3. Also, the mouse chimeric antibodies were prepared, and then conjugates of the antibodies with the resiquimod derivative were prepared in the same way as in Example 4.

[0264]

Specifically, the following antibodies were used in this Example as the mouse chimeric antibodies comprising the light chain variable regions of the anti-CAPRIN-1 monoclonal antibodies and the light chain constant region of mouse IgG.

[0265]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 40, SEQ ID NO: 41, and SEQ ID NO: 42, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 39 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 43 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0266]

The monoclonal antibody against CAPRIN-1 disclosed in WO2015/020212, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 44, SEQ ID NO: 45, and SEQ ID NO: 46, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively,

and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 47 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 51 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0267]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096519, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 52, SEQ ID NO: 53, and SEQ ID NO: 54, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 56, SEQ ID NO: 57, and SEQ ID NO: 58, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 55 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 59 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0268]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125654, wherein the antibody comprises CDR1, CDR2, and CDR3 of heavy chain variable region consisting of the amino acid sequences of SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively, and CDR1, CDR2, and CDR3 of light chain variable region consisting of the amino acid sequences of SEQ ID NO: 64, SEQ ID NO: 65, and SEQ ID NO: 66, respectively, and wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by SEQ ID NO: 63 comprising the above-mentioned CDR1, CDR2, and CDR3 of heavy chain variable region, and the amino acid sequence of a light chain variable region represented by SEQ ID NO: 67 comprising the above-mentioned CDR1, CDR2, and CDR3 of light chain variable region.

[0269]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096517, the

antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69.

[0270]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096528, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79.

[0271]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096533, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 80 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 81, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 82 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 83.

[0272]

The monoclonal antibody against CAPRIN-1 disclosed in WO2011/096534, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 84 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 85, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 86 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 87.

[0273]

The monoclonal antibody against CAPRIN-1 disclosed in WO2010/016526, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 88 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 89; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 90 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 91; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 92 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 93; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 94 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 95; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 96 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 97; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 98 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 99; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 100 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 101.

[0274]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018894, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 102 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 103, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 104 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 105.

[0275]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018892, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 106 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 107.

[0276]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018891, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 108 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 109.

[0277]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018889, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 110 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 111.

[0278]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/018883, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 112 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 113.

[0279]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125636, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 114 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 115.

[0280]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125654, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 116 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 117, or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 118 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 119.

[0281]

The monoclonal antibody against CAPRIN-1 disclosed in WO2013/125630, the antibody comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 120 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 121.

[0282]

The monoclonal antibody against CAPRIN-1 disclosed in WO2015/020212, wherein the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 122 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 123; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 124 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 125; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence

of SEQ ID NO: 128 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 129; the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131; or the antibody comprises the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133.

[0283]

The mouse chimeric antibodies were prepared by the following method.

[0284]

Specifically, an amplification fragment of a gene encoding a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 39 according to the present invention was treated at its both ends with restriction enzymes, then purified, and inserted into a vector already comprising inserts of a human antibody-derived leader sequence and the heavy chain constant region of mouse IgG, according to an ordinary method. Further, an amplification fragment of a gene encoding a light chain variable region having the amino acid sequence represented by SEQ ID NO: 43 was treated at its both ends with restriction enzymes, then purified, and inserted into a vector already comprising inserts of a human antibody-derived leader sequence and the light chain constant region of mouse IgG, according to an ordinary method.

[0285]

Next, the recombinant vector having a gene insert of the heavy chain variable region of the antibody against CAPRIN-1 as described above and the recombinant vector having a gene insert of the light chain variable region of the antibody, were transferred to mammalian cells according to an ordinary method, and a solution containing mouse chimeric antibody #1 composed of a heavy chain comprising the heavy chain variable region of the antibody against CAPRIN-1 represented by SEQ ID NO: 39 and the heavy chain constant region of mouse IgG, and a light chain comprising the light chain variable region represented by SEQ ID NO: 43 of

the antibody against CAPRIN-1 and the light chain constant region of mouse IgG.

[0286]

A solution containing mouse chimeric antibody #2 composed of a heavy chain comprising a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 47 and the heavy chain constant region of mouse IgG, and a light chain comprising a light chain variable region having the amino acid sequence represented by SEQ ID NO: 51 and the light chain constant region of mouse IgG was prepared in a similar way.

[0287]

A solution containing mouse chimeric antibody #3 composed of a heavy chain comprising a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 55 and the heavy chain constant region of mouse IgG, and a light chain comprising a light chain variable region having the amino acid sequence represented by SEQ ID NO: 59 and the light chain constant region of mouse IgG was prepared in a similar way.

[0288]

A solution containing mouse chimeric antibody #4 composed of a heavy chain comprising a heavy chain variable region having the amino acid sequence represented by SEQ ID NO: 63 and the heavy chain constant region of mouse IgG, and a light chain comprising a light chain variable region having the amino acid sequence represented by SEQ ID NO: 67 and the light chain constant region of mouse IgG was prepared in a similar way.

[0289]

Solutions containing the following mouse chimeric antibodies #5 to #37 were prepared in a similar way.

[0290]

Mouse chimeric antibody #5 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 68 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 69 and the light chain constant region of mouse IgG.

[0291]

Mouse chimeric antibody #6 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 70 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 71 and the light chain constant region of mouse IgG.

[0292]

A solution containing mouse chimeric antibody #7 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 72 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 73 and the light chain constant region of mouse IgG.

[0293]

Mouse chimeric antibody #8 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 74 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 75 and the light chain constant region of mouse IgG.

[0294]

Mouse chimeric antibody #9 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 76 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 77 and the light chain constant region of mouse IgG.

[0295]

Mouse chimeric antibody #10 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 78 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 79 and the light chain constant region of mouse IgG.

[0296]

Mouse chimeric antibody #11 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 80 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 81 and the light chain constant region of mouse IgG.

[0297]

Mouse chimeric antibody #12 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 82 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 83 and the light chain constant region of mouse IgG.

[0298]

Mouse chimeric antibody #13 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 84 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 85 and the light chain constant region of mouse IgG.

[0299]

Mouse chimeric antibody #14 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 86 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 87 and the light chain constant region of mouse IgG.

[0300]

Mouse chimeric antibody #15 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 88 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence

of SEQ ID NO: 89 and the light chain constant region of mouse IgG.

[0301]

Mouse chimeric antibody #16 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 90 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 91 and the light chain constant region of mouse IgG.

[0302]

Mouse chimeric antibody #17 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 92 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 93 and the light chain constant region of mouse IgG.

[0303]

Mouse chimeric antibody #18 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 94 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 95 and the light chain constant region of mouse IgG.

[0304]

Mouse chimeric antibody #19 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 96 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 97 and the light chain constant region of mouse IgG.

[0305]

Mouse chimeric antibody #20 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 98 and the heavy chain constant region of mouse IgG, and a light chain comprising the

amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 99 and the light chain constant region of mouse IgG.

[0306]

Mouse chimeric antibody #21 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 100 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 101 and the light chain constant region of mouse IgG.

[0307]

Mouse chimeric antibody #22 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 102 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 103 and the light chain constant region of mouse IgG.

[0308]

Mouse chimeric antibody #23 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 104 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 105 and the light chain constant region of mouse IgG.

[0309]

Mouse chimeric antibody #24 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 106 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 107 and the light chain constant region of mouse IgG.

[0310]

Mouse chimeric antibody #25 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID

NO: 108 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 109 and the light chain constant region of mouse IgG.

[0311]

Mouse chimeric antibody #26 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 110 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 111 and the light chain constant region of mouse IgG.

[0312]

Mouse chimeric antibody #27 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 112 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 113 and the light chain constant region of mouse IgG.

[0313]

Mouse chimeric antibody #28 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 114 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 115 and the light chain constant region of mouse IgG.

[0314]

Mouse chimeric antibody #29 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 116 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 117 and the light chain constant region of mouse IgG.

[0315]

Mouse chimeric antibody #30 composed of a heavy chain comprising the amino acid

sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 118 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 119 and the light chain constant region of mouse IgG.

[0316]

Mouse chimeric antibody #31 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 120 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 121 and the light chain constant region of mouse IgG.

[0317]

Mouse chimeric antibody #32 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 122 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 123 and the light chain constant region of mouse IgG.

[0318]

Mouse chimeric antibody #33 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 124 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 125 and the light chain constant region of mouse IgG.

[0319]

Mouse chimeric antibody #34 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 126 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 127 and the light chain constant region of mouse IgG.

[0320]

Mouse chimeric antibody #35 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 128 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 129 and the light chain constant region of mouse IgG.

[0321]

Mouse chimeric antibody #36 composed of a heavy chain comprising the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 130 and the heavy chain constant region of mouse IgG, and a light chain comprising the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 131 and the light chain constant region of mouse IgG.

[0322]

Mouse chimeric antibody #37 composed of a heavy chain having the amino acid sequence of a heavy chain variable region represented by the amino acid sequence of SEQ ID NO: 132 and the heavy chain constant region of mouse IgG, and a light chain having the amino acid sequence of a light chain variable region represented by the amino acid sequence of SEQ ID NO: 133 and the light chain constant region of mouse IgG.

[0323]

The prepared culture supernatant containing each of mouse chimeric antibodies #1 to #37 was purified according to a conventional method using Hitrap Protein A Sepharose FF (GE Healthcare Japan Corp.). The buffer was replaced with PBS(-), and the resultant was filtered through a 0.22 μm filter (Merck Millipore Corp.) to prepare the mouse chimeric antibodies.

[0324]

Conjugates with resiquimod were prepared in the same way as the method described in Example 3 using mouse chimeric antibodies #1 to #37 prepared above. Solutions containing a conjugate of mouse chimeric antibody #1 with resiquimod (Conjugate 29), a conjugate of mouse chimeric antibody #2 with resiquimod (Conjugate 30), a conjugate of mouse chimeric antibody #3 with resiquimod (Conjugate 31), a conjugate of mouse chimeric antibody #4 with

resiquimod (Conjugate 32), a conjugate of mouse chimeric antibody #5 with resiquimod (Conjugate 177), a conjugate of mouse chimeric antibody #6 with resiquimod (Conjugate 178), a conjugate of mouse chimeric antibody #7 with resiquimod (Conjugate 179), a conjugate of mouse chimeric antibody #8 with resiquimod (Conjugate 180), a conjugate of mouse chimeric antibody #9 (Conjugate 181), a conjugate of mouse chimeric antibody #10 with resiquimod (Conjugate 182), a conjugate of mouse chimeric antibody #11 with resiquimod (Conjugate 183), a conjugate of mouse chimeric antibody #12 with resiquimod (Conjugate 184), a conjugate of mouse chimeric antibody #13 with resiquimod (Conjugate 185), a conjugate of mouse chimeric antibody #14 with resiquimod (Conjugate 186), a conjugate of mouse chimeric antibody #15 with resiquimod (Conjugate 187), a conjugate of mouse chimeric antibody #16 with resiquimod (Conjugate 188), a conjugate of mouse chimeric antibody #17 with resiquimod (Conjugate 189), a conjugate of mouse chimeric antibody #18 with resiquimod (Conjugate 190), a conjugate of mouse chimeric antibody #19 with resiquimod (Conjugate 191), a conjugate of mouse chimeric antibody #20 with resiquimod (Conjugate 192), a conjugate of mouse chimeric antibody #21 with resiquimod (Conjugate 193), a conjugate of mouse chimeric antibody #22 with resiquimod (Conjugate 194), a conjugate of mouse chimeric antibody #23 with resiquimod (Conjugate 195), a conjugate of mouse chimeric antibody #24 with resiquimod (Conjugate 196), a conjugate of mouse chimeric antibody #25 with resiquimod (Conjugate 197), a conjugate of mouse chimeric antibody #26 with resiquimod (Conjugate 198), a conjugate of mouse chimeric antibody #27 with resiquimod (Conjugate 199), a conjugate of mouse chimeric antibody #28 with resiquimod (Conjugate 200), a conjugate of mouse chimeric antibody #29 with resiquimod (Conjugate 201), a conjugate of mouse chimeric antibody #30 with resiquimod (Conjugate 202), a conjugate of mouse chimeric antibody #31 with resiquimod (Conjugate 203), a conjugate of mouse chimeric antibody #32 with resiquimod (Conjugate 204), a conjugate of mouse chimeric antibody #33 with resiquimod (Conjugate 205), a conjugate of mouse chimeric antibody #34 with resiquimod (Conjugate 206), a conjugate of mouse chimeric antibody #35 with resiquimod (Conjugate 207), a conjugate of mouse chimeric antibody #36 with resiquimod (Conjugate 208), and a conjugate of mouse chimeric antibody #37 with resiquimod

(Conjugate 209) were prepared.

[0325]

Further, conjugates with the resiquimod derivative were prepared in the same way as the method described in Example 4 using mouse chimeric antibodies #1 to #37 prepared above. Solutions containing a conjugate of mouse chimeric antibody #1 with the resiquimod derivative (Conjugate 33), a conjugate of mouse chimeric antibody #2 with the resiquimod derivative (Conjugate 34), a conjugate of mouse chimeric antibody #3 with the resiquimod derivative (Conjugate 35), and a conjugate of mouse chimeric antibody #4 with the resiquimod derivative (Conjugate 36) were prepared. Solutions containing conjugates of mouse chimeric antibodies #5 to #37 with the resiquimod derivative (Conjugates 210 to 242) were prepared in a similar way.

[0326]

The prepared solutions containing Conjugates 29 to 36, Conjugates 177 to 242, and Control conjugate 2 were each filtered through a 0.22 μm filter (manufactured by Merck Millipore Corp.) to prepare the conjugates.

[0327]

Conjugates 29 to 36 and Conjugates 177 to 242 were assayed for their specific reactivity with the CAPRIN-1 protein in the same way as in Example 5 using the prepared solutions containing Conjugates 29 to 36 and Conjugates 177 to 242. As a result, the solutions containing Conjugates 29 to 36 and Conjugates 177 to 242 each exhibited specific reactivity with the CAPRN-1 protein.

[0328]

Further, Conjugates 29 to 36 and Conjugates 177 to 242 were assayed for their reactivity with cancer cells by flow cytometry using the cancer cells expressing CAPRIN-1 on the cell membrane surface. As a result, all the conjugates exhibited stronger fluorescence intensity than that of the negative control. Also, the conjugates were found to exhibit strong reactivity equivalent to that of the anti-CAPRIN-1 monoclonal antibodies described in mouse chimeric antibodies #1 to #37 prepared above, unconjugated with the immune activator.

[0329]

Example 9 Antitumor effect of conjugate of mouse chimeric anti-CAPRIN-1 monoclonal antibody and immune activator

The conjugates of the mouse chimeric anti-CAPRIN-1 monoclonal antibodies and the immune activator (Conjugates 29 to 36 and conjugates 177 to 242) prepared in Example 8 were evaluated for their *in vivo* antitumor effects of the antibodies on cancer-bearing mice.

[0330]

Specifically, the conjugates of the present invention were examined for their antitumor effect using Balb/c mice in which mouse-derived cancer cells expressing CAPRIN-1 were transplanted. Mouse breast cancer cells 4T1 were subcutaneously transplanted at 10^4 cells/mouse to the ventral regions of the mice, which were then grown until tumor became 30 mm^3 or larger to prepare cancer-bearing mice. As shown in Example 5, the breast cancer cells 4T1 are cells expressing the CAPRIN-1 protein on the cell membrane surface. The solutions containing Conjugates 29 to 36 prepared in Example 8 each specifically bind to CAPRIN-1 on the cell membrane surface of the breast cancer cells 4T1. Conjugates 29 to 36 prepared in Example 8 were each administered at 8 mg/kg to the tail veins of 10 cancer-bearing mice. Mouse chimeric antibodies #1 to #4 were each administered as a comparative control in the same amount as above to the cancer-bearing mice. The administration was carried out twice a week a total of four times. PBS(-) was administered to cancer-bearing mice, for a negative control. The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor) x (Length of the minor axis of tumor)^2 x 0.5. As a result, all the mice given Conjugates 29 to 36 had 0% tumor volume 20 days after the start of the administration relative to the tumor volume of the negative control (100%). Also, the mice given mouse chimeric antibodies #1 to #4 alone had 69% tumor volume on average relative to the tumor volume of the negative control mice (100%). These evaluation results demonstrated that the conjugates of resiquimod and the mouse chimeric anti-CAPRIN-1 antibodies (mouse chimeric antibodies) (Conjugates 29 to 32) and the conjugates of the resiquimod derivative and these antibodies (Conjugates 33 to 36) prepared in Example 8 exert a stronger antitumor effect as compared

with the negative control and the case of administering the anti-CAPRIN-1 antibody alone to cancer-bearing mice. As a result of similarly evaluating Conjugates 177 to 242 for their antitumor effects, all the mice given Conjugates 29 to 36 had 0% tumor volume relative to the tumor volume of the negative control (100%). The mice given mouse chimeric antibodies #5 to #37 alone had 69% tumor volume on average relative to the tumor volume of the negative control (100%).

[0331]

Example 10 Antitumor effect of conjugate - 3

An *in vivo* antitumor effect on cancer-bearing mice was compared between Conjugates 7 to 14, Conjugates 21 to 28, and Conjugates 45 to 179 prepared in Example 4 using the anti-CAPRIN-1 monoclonal antibodies, and a trastuzumab conjugate prepared in the same way as in Example 4 using the existing antibody drug trastuzumab for a cancer, or trastuzumab.

[0332]

The trastuzumab conjugate is a conjugate prepared in the same way as in Example 4 using trastuzumab and the immune activator. The conjugate of trastuzumab and the immune activator was prepared by the following method.

[0333]

With reference to J. Med. Chem. 2008, 51, 6916-6926, succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) was condensed with 1-(2(2-aminoethoxy)-2-methylpropyl)-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-4-amine, a resiquimod derivative made by two-carbon homologation of the tertiary hydroxy group of resiquimod and the addition of an amino group thereto to obtain a condensate of resiquimod bound with SMCC, as the immune activator.

[0334]

Meanwhile, trastuzumab was used in the preparation of the conjugate after removing a formulation composition contained in a solution using an ultrafilter, or affinity-purifying only trastuzumab using a protein A carrier and adding the trastuzumab to a phosphate buffer. A conjugate of the condensate of resiquimod with the linker SMCC as described above and an anti-CAPRIN-1 antibody was prepared according to an ordinary method with reference to the

methods described in U.S. Patent No. 8,951,528 and JIMD Reports-Case and Research Reports, 2012/5. Using the trastuzumab dissolved in a phosphate buffer, a solution containing SATA-added trastuzumab was obtained in the same way as in Example 4. This solution was further reacted with the condensate prepared above to prepare a solution containing a conjugate of trastuzumab and the resiquimod derivative (trastuzumab conjugate). The obtained trastuzumab conjugate was verified by flow cytometry to exhibit reactivity with human breast cancer cells used in the antitumor effect evaluation. It was further verified by mass spectrometry that the prepared trastuzumab conjugate to be compared, and Conjugates 7 to 14, Conjugates 21 to 28, and Conjugates 45 to 179 prepared in Example 4 using the anti-CAPRIN-1 monoclonal antibodies, have comparable molecule numbers of the immune activator bound therein and the verified conjugates were used in the following evaluation.

[0335]

For the comparison of the antitumor effect, human breast cancer cells BT474 were mixed with Matrigel (Sigma-Aldrich Corp.) and subcutaneously transplanted at 10^7 cells/mouse to the mice, which were then grown until tumor became 150 mm^3 or larger to prepare cancer-bearing mice. BT474 has been found to express the CAPRIN-1 protein and HER2, which is a target antigen of trastuzumab, on the cell membrane surface.

[0336]

The conjugates of the anti-CAPRIN-1 antibody (Conjugates 7 to 14, Conjugates 21 to 28, and Conjugates 45 to 179) and the trastuzumab conjugate prepared above were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice. The administration was carried out twice a week a total of 13 times. For comparison, the anti-CAPRIN-1 antibodies used in the preparation of the conjugates of the anti-CAPRIN-1 antibody (Conjugates 7 to 14, conjugates 21 to 28, and conjugates 45 to 179), and trastuzumab were administered in the same way as above. PBS(-) was administered to cancer-bearing mice, for a negative control.

[0337]

The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor) x (Length of the minor axis of

tumor)^2 x 0.5. As a result of the evaluation, all the mice given Conjugates 11 and 25 had less than 15% tumor volumes 45 days after the start of the administration relative to the tumor volume of the negative control (100%). The mice given the unconjugated anti-CAPRIN-1 antibodies to be compared had less than 50% tumor volume. From these results, it was shown that the conjugation of the immune activator to the anti-CAPRIN-1 antibody enhanced the antitumor effect of the antibody by 77%. The rate of enhancement was calculated based on the expression: 1 - (Tumor volume determined with conjugate / Tumor volume determined with antibody alone) x 100 (%).

[0338]

On the other hand, the mice given the trastuzumab conjugate and the mice given the unconjugated trastuzumab to be compared had 53% and 74% tumor volumes, respectively, relative to the tumor volume of the negative control (100%). Thus, the rate of enhancement in antitumor effect by the conjugation of the immune activator to trastuzumab was only less than 29%.

[0339]

Example 11 Preparation of conjugate of anti-CAPRIN-1 antibody and immune activator and antitumor effect of the conjugate

Conjugates of humanized antibodies #1 to #8 which were the anti-CAPRIN-1 monoclonal antibodies described in Example 2 with an immune activator DSR-6434 (6-amino-2(butylamino)-9-[[6-[2-(dimethylamino)ethoxy]-3-pyridinyl]methyl]-7,9-dihydro-8H-purin-8-one) (Conjugate 37 to 44) were prepared. Specifically, a condensate of DSR-6434 with succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) via the amino group of DSR-6434 was first synthesized, and then, solutions containing conjugates of humanized antibodies #1 to #8 and the immune activator RSR-6434 (Conjugates 37 to 44) were prepared basically according to the method described in Example 4.

[0340]

The prepared solutions containing Conjugates 37 to 44 were each filtered through a 0.22 μm filter (Merck Millipore Corp.) to prepare the conjugates. The conjugates were assayed for their specific reactivity with the CAPRIN-1 protein in the same way as in Example

5. As a result, the solutions containing Conjugates 37 to 44 each exhibited specific reactivity with the CAPRN-1 protein.

[0341]

Conjugates 37 to 44 were further assayed for their reactivity with cancer cells by flow cytometry using cancer cells expressing the CAPRIN-1 protein on the cell membrane surface. As a result, all the conjugates exhibited stronger fluorescence intensity than that of the negative control. The conjugates were found to exhibit fluorescence intensity similar to that of the antibodies alone used in the conjugates.

[0342]

Conjugates 37 to 44 were evaluated for their antitumor effects on cancer-bearing mice. The conjugates of anti-CAPRIN-1 antibody (Conjugates 37 to 44) were each administered at 10 mg/kg to the tail veins of 10 cancer-bearing mice in the same way as the method described in Example 10. The administration was carried out twice a week a total of 16 times. The anti-CAPRIN-1 antibodies used in the preparation of the conjugates were administered in the same way as above. PBS(-) was administered to cancer-bearing mice, for a negative control.

[0343]

The tumor sizes of the cancer-bearing mice after the administration were measured using calipers over time, and tumor volumes were calculated according to an ordinary method based on the expression: (Length of the major axis of tumor) x (Length of the minor axis of tumor)^2 x 0.5. As a result of the evaluation, all the mice given Conjugates 37 to 44 had less than 32% tumor volumes 50 days after the start of the administration relative to the tumor volume of the negative control (100%). The mice given the unconjugated anti-CAPRIN-1 antibodies to be compared had less than 50% tumor volume. From these results, the conjugation of the immune activator to the anti-CAPRIN-1 antibody was shown to enhance the antitumor effect by more than 35%. The rate of enhancement was calculated based on the expression: 1 - (Tumor volume determined with conjugate / Tumor volume determined with antibody alone) x 100 (%).

[0344]

Throughout this specification and the claims which follow, unless the context requires

otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0345] The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

Claims

1. A conjugate of an antibody or a fragment thereof linked to an immune activator, wherein the antibody or the fragment thereof specifically binds to a CAPRIN-1 protein having an amino acid sequence represented by any of even-numbered SEQ ID NOs among SEQ ID NOs: 2 to 30 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence, wherein the immune activator is a Toll-like receptor (TLR) 7- or 8-binding ligand or agonist, and wherein the CAPRIN-1 protein is expressed on a cancer cell.

2. The conjugate according to claim 1, wherein the antibody or the fragment thereof specifically binds to a partial polypeptide of the CAPRIN-1 protein, wherein the partial polypeptide has an amino acid sequence represented by any of SEQ ID NOs: 31 to 35 and 296 to 299, 308, and 309 or an amino acid sequence having 80% or more sequence identity to the amino acid sequence, and wherein the CAPRIN-1 protein is expressed on a cancer cell.

3. The conjugate according to claim 1 or 2, wherein the antibody is a monoclonal antibody or a polyclonal antibody.

4. The conjugate according to any one of claims 1 to 3, wherein the antibody or the fragment thereof is any of the following (A) to (M):

(A) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(B) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(C) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(D) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(E) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(F) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(G) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(H) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(I) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(J) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(K) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein,

(L) an antibody or a fragment thereof, which comprises a heavy chain variable region comprising complementarity-determining regions of SEQ ID NOs: 300, 301, and 302 (CDR1, CDR2, and CDR3, respectively) and a light chain variable region comprising complementarity-determining regions of SEQ ID NOs: 304, 305, and 306 (CDR1, CDR2, and CDR3, respectively) and has immunological reactivity with the CAPRIN-1 protein, and

(M) an antibody or a fragment thereof, which comprises 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 has immunological reactivity with the CAPRIN-1 protein.

5. The conjugate according to any one of claims 1 to 4, wherein the antibody or the fragment

thereof is any 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: 303 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 307.

6. The conjugate according to any one of claims 1 to 5, wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, or a single-chain antibody.

7. The conjugate according to any one of claims 1 to 6, wherein the TLR7- or TLR8-binding ligand or agonist is selected from the group consisting of an imidazoquinoline compound and single-stranded RNA.

8. The conjugate according to any one of claims 1 to 7, wherein the antibody or the fragment thereof is linked to the immune activator via a linker.

9. A pharmaceutical composition when used for treatment and/or prevention of a cancer expressing a CAPRIN-1 protein on the cell membrane surface, comprising the conjugate according to any one of claims 1 to 8 as an active ingredient.

10. The pharmaceutical composition according to claim 9, wherein the cancer is breast cancer, kidney cancer, pancreatic cancer, colorectal cancer, lung cancer, brain tumor, stomach cancer, uterine cancer, ovary cancer, prostate cancer, bladder cancer, esophagus cancer, leukemia, lymphoma, liver cancer, gallbladder cancer, sarcoma, mastocytoma, melanoma, adrenal cortex cancer, Ewing's tumor, Hodgkin's lymphoma, mesothelioma, multiple myeloma, testicle cancer, thyroid cancer, or head and neck cancer.

11. A method for treating and/or preventing a cancer expressing a CAPRIN-1 protein on the cell membrane surface, comprising administering the conjugate according to any one of claims 1 to 8 or the pharmaceutical composition according to claim 9 or 10 to a subject.

12. A conjugate according to any one of claims 1 to 8, or a pharmaceutical composition according to claim 9 or 10, when used in treatment and/or prevention of a cancer expressing a CAPRIN-1 protein on the cell membrane surface.

13. Use of a conjugate according to any one of claims 1 to 8, or a pharmaceutical composition according to claim 9 or 10, in the manufacture of a medicament for treatment and/or prevention of a cancer expressing a CAPRIN-1 protein on the cell membrane surface.

SEQUENCE LISTING

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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
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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
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Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu
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Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu
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cca att gat cag att cag gca aca atc tct tta aat aca gac cag act       1623
Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr
        465                 470                 475

aca gca tca tca tcc ctt cct gct gcg tct cag cct caa gta ttt cag       1671
Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln
    480                 485                 490

gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta aat gca       1719
Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala
495                 500                 505                 510

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Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val
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cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag tac cag       1815
Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln
            530                 535                 540

gcc agt tat aac cag agc ttt tct agt cag cct cac caa gta gaa caa       1863
Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln
        545                 550                 555

aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act tac cat       1911
Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His
    560                 565                 570

ggt tcc cca gac cag tcc cat caa gtg act ggt aac cac cag cag cct       1959
Gly Ser Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro
575                 580                 585                 590

cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat tac aat       2007
Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn
                595                 600                 605

agt cgt ggt gtg tct cgt gga ggc tcc cgt ggt gct aga ggc ttg atg       2055
Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met
            610                 615                 620

aat gga tac cgg ggc cct gcc aat gga ttc aga gga gga tat gat ggt       2103
Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly
        625                 630                 635

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
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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
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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 cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg caa       2295
Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln
            690                 695                 700

atg aac act cag caa gtg aat taa tctgattcac aggattatgt ttaatcgcca      2349
Met Asn Thr Gln Gln Val Asn
        705

aaaacacact ggccagtgta ccataatatg ttaccagaag agttattatc tatttgttct     2409

ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca ggactacaat     2469

tgtcagcttt ctattacctg gatatggaag gaaactattt ttactctgca tgttctgtcc     2529

taagcgtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc ttaggagtaa     2589

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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
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Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Ala Val Glu Asp Gln Val
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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
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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
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Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn
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Thr Gln Gln Val Asn
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ggaagggacc gccacccttg ccccctcagc tgcccactcg tgatttccag cggcctccgc      180

gcgcgcacg atg ccc tcg gcc acc agc cac agc ggg agc ggc agc aag tcg      231
          Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser
          1               5                  10

tcc gga ccg cca ccg ccg tcg ggt tcc tcc ggg agt gag gcg gcc gcg        279
Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala
15                  20                  25                  30

gga gcc ggg gcc gcc gcg ccg gct tct cag cac ccc gca acc ggc acc        327
Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr
                35                  40                  45

ggc gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg atc gac        375
Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp
            50                  55                  60

aag aaa ctt cgg aac ctg gag aag aaa aag ggt aag ctt gat gat tac        423
Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr
        65                  70                  75

cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag ctg gat        471
Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu Asp
    80                  85                  90

gcc gtt tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca aaa        519
Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala Lys
95                  100                 105                 110

gaa tta cag agg agt ttc atg gca cta agt caa gat att cag aaa aca        567
Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr
                115                 120                 125

ata aag aag aca gca cgt cgg gag cag ctt atg aga gaa gaa gct gaa        615
Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu
            130                 135                 140

cag aaa cgt tta aaa act gta ctt gag cta cag tat gtt ttg gac aaa        663
Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp Lys
        145                 150                 155

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
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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       1479
Ser Arg Leu Ala Gln Pro Asn Gln Val Pro Val Gln Pro Glu Ala Thr
415                 420                 425                 430

cag gtt cct ttg gta tca tcc aca agt gag ggg tac aca gca tct caa       1527
Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln
                435                 440                 445

ccc ttg tac cag cct tct cat gct aca gag caa cga cca cag aag gaa       1575
Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu
            450                 455                 460

cca att gat cag att cag gca aca atc tct tta aat aca gac cag act       1623
Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr
        465                 470                 475

aca gca tca tca tcc ctt cct gct gcg tct cag cct caa gta ttt cag       1671
Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln
    480                 485                 490

gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta aat gca       1719
Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala
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495                 500                 505                 510

gct cca ttc caa tcc atg caa acg gtg ttc aat atg aat gcc cca gtt       1767
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                515                 520                 525

cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag tac cag       1815
Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln Tyr Gln
            530                 535                 540

gcc agt tat aac cag agc ttt tct agt cag cct cac caa gta gaa caa       1863
Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln
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aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act tac cat       1911
Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr Tyr His
    560                 565                 570

ggt tcc cca gac cag tcc cat caa gtg act ggt aac cac cag cag cct       1959
Gly Ser Pro Asp Gln Ser His Gln Val Thr Gly Asn His Gln Gln Pro
575                 580                 585                 590

cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat tac aat       2007
Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr Tyr Asn
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agt cgt ggt gtg tct cgt gga ggc tcc cgt ggt gct aga ggc ttg atg       2055
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Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly
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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
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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

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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
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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
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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
gtcacaaata acttggagtt tgcaaaagaa ttacagagga gtttc atg gca tta agt       57
                                                 Met Ala Leu Ser
                                                 1

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 tcg        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
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        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 ggt 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       1161
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
            360                 365                 370

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1209
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
        375                 380                 385

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1257
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
    390                 395                 400
```

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aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa       1305
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
405                 410                 415                 420

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag       1353
Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln
                425                 430                 435

cct cac caa gta gaa caa aca gag gga tgc cgc aaa tga acactcagca        1402
Pro His Gln Val Glu Gln Thr Glu Gly Cys Arg Lys
            440                 445

agtgaattaa tctgattcac aggattatgt ttaaacgcca aaaacacact ggccagtgta     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
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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

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag        144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag        192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag        240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt        288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
                85                  90                  95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat        336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
            100                 105                 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt        384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt        432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc        480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg        528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175
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aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg        576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc        624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac        672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca        720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc        768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca        816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

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 ggt gaa aag gag cag        960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag       1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

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
                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
            420                 425                 430
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gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag       1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag       1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct       1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct       1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa       1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag       1680
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

tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag       2064
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
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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 ggccagtgta ccataatatg     2214

ttaccagaag agttattatc tatttgttct ccctttcagg aaacttattg taaagggact     2274

gttttcatcc cataaagaca ggactacaat tgtcagcttt atattacctg gatatggaag     2334

gaaactattt ttattctgca tgttcttcct aagcgtcatc ttgagccttg cacatgatac     2394

tcagattcct cacccttgct taggagtaaa acataataca ctttacaggg tgatatctcc     2454

atagttattt gaagtggctt ggaaaaagca agattaactt ctgacattgg ataaaaatca     2514

acaaatcagc cctagagtta ttcaaatggt aattgacaaa aactaaaata tttcccttcg     2574

agaaggagtg gaatgtggtt tggcagaaca actgcatttc acagcttttc cggttaaatt     2634

ggagcactaa acgtttagat gcataccaaa ttatgcatgg gcccttaata taaaaggctg     2694

gctaccagct ttgacacagc actattcatc ctctggccaa acaactgtgg ttaaacaaca     2754

catgtaaatt gctttttaac agctgatact ataataagac aaagccaaaa tgcaaaaatt     2814

gggctttgat tggcactttt tgaaaaatat gcaacaaata tgggatgtaa tctggatggc     2874

cgcttctgta cttaatgtga agtatttaga tacctttttg aacacttaac agtttcttct     2934

gacaatgact tttgtaagga ttggtactat ctatcattcc ttataatgta cattgtctgt     2994

cactaatcct cagatcttgc tgtattgtca cctaaattgg tacaggtact gatgaaaata     3054

tctaatggat aatcataaca ctcttggtca catgtttttc ctgcagcctg aaggttttta     3114

aaagaaaaag atatcaaatg cctgctgcta ccacccttttt aaattgctat cttttgaaaa     3174

gcaccagtat gtgttttaga ttgatttccc tattttaggg aaatgacaga cagtagtttc     3234

agttctgatg gtataagcaa aacaaataaa acatgtttat aaaagttgta tcttgaaaca     3294

ctggtgttca acagctagca gcttatgtgg ttcaccccat gcattgttag tgtttcagat     3354

tttatggtta tctccagcag ctgtttctgt agtacttgca tttatctttt gtctaaccct     3414

aatattctca cggaggcatt tatattcaaa gtggtgatcc cttcacttag acgcataggg     3474

agagtcacaa gtttgatgaa gaggacagtg tagtaattta tatgctgttg gaatttgtgc     3534

tagcagtttg agcactagtt ctgtgtgcct atgaacttaa tgctgcttgt catattccac     3594

tttgacttca tggagaatta atcccatcta ctcagcaaag gctatactaa tactaagtta     3654

atggtatttt ctgtgcagaa attgaatttt gttttattag catttagcta aggaattttt     3714

ccagtaggtg ctcagctact aaagaaaaac aaaaacaaga cacaaaacta ttctcaaaca     3774

ttcattgtta gacaactgga gtttttgctg gttttgtaac ctactaaaat ggataggctg     3834

ttgaacattc cacattcaaa agttttttgt agggtggtgg ggaaggggggg gtgtcttcaa     3894
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tgtttatttt aaaataaaat aagttcttga cttttctcat gtgtggttgt ggtacatcat 3954

attggaaggg ttatctgttt acttttgcaa atgagtattt ctcttgctag cacctcccgt 4014

tgtgcgcttt aaatgacatc tgcctgggat gtaccacaac catatgttag ctgtatttta 4074

tggggaatag ataaaatatt cgtggtttat tgggtaatcc ctagatgtgt atgcttacaa 4134

tcctatatat aaaactaaat 4154

<210> 8
<211> 717
<212> PRT
<213> Canis familiaris

<400> 8

Met Pro Ser Ala Thr Ser Leu 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 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
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
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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 Arg Gly Gly Pro Pro Arg Pro
    690                 695                 700

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

<210> 9
<211> 4939
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(2109)

<400> 9

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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

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag        144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag        192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag        240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt        288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
                85                  90                  95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat        336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
            100                 105                 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt        384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt        432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc        480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg        528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg        576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc        624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205
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ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac        672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca        720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc        768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca        816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

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 ggt gaa aag gag cag        960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag       1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

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
                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
            420                 425                 430

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag       1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag       1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460
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caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct       1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct       1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa       1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag       1680
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

tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag       2064
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 aat att ttg tgg tgg tga           2109
Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn Ile Leu Trp Trp
    690                 695                 700

tcctagctcc taagtggagc ttctgttctg gccttggaag agctgttcca tagtctgcat     2169

gtaggttaca tgttaggaat acatttatca ttaccagact tgttgctagg gattaaatga     2229

aatgctctgt ttctaaaact tctcttgaac ccaaatttaa ttttttgaat gactttccct     2289
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gttactatat aaattgtctt gaaaactaga acatttctcc tcctcagaaa aagtgttttt 2349

ccaactgcaa attatttttc aggtcctaaa acctgctaaa tgtttttagg aagtacttac 2409

tgaaacattt ttgtaagaca tttttggaat gagattgaac atttatataa atttattatt 2469

attcctcttt cattttgaa catgcatatt atattttagg gtcagaaatc ctttaatggc 2529

caaataagcc atagttacat ttagagaacc atttagaagt gatagaacta actgaaattt 2589

caatgccttt ggatcattaa tagcgatata aatttcaaat tgtttctgac ttttaaataa 2649

aacatccaaa atcctaacta acttcctgaa ctatatttaa aaattacagg tttaaggagt 2709

ttctggtttt ttttctctta ccataggaaa actgtttcct gtttggccag gaagtcaacc 2769

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cttcactgct gtatctattt ccaacgcctg atgacagtgc ctgacacata gtaggcactc 3369

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tacactttac agggtgatat ctccatagtt atttgaagtg gcttggaaaa agcaagatta 4029

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caaaaactaa aatatttccc ttcgagaagg agtggaatgt ggtttggcag aacaactgca 4149

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ccaaacaact gtggttaaac aacacatgta aattgctttt taacagctga tactataata 4329

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ccatgcattg ttagtgtttc agattttatg gttatctcca gcagctgttt ctgtagtact 4929

tgcatttatc 4939

<210> 10
<211> 702
<212> PRT
<213> Canis familiaris

<400> 10

Met Pro Ser Ala Thr Ser Leu 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 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

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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
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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
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                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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<210> 11
<211> 3306
<212> DNA
<213> Canis familiaris

<220>
<221> CDS
<222> (1)..(2040)

<400> 11

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

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

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag        144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag        192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag        240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt        288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
                85                  90                  95

aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat        336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
            100                 105                 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt        384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt        432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc        480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160
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cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg        528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg        576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc        624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac        672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca        720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc        768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca        816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

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 ggt gaa aag gag cag        960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag       1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

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
                405                 410                 415
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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

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag       1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag       1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct       1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct       1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa       1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag       1680
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

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

aggattatgt ttaaacgcca aaaacacact ggccagtgta ccataatatg ttaccagaag 2130

agttattatc tatttgttct ccctttcagg aaacttattg taaagggact gttttcatcc 2190

cataaagaca ggactacaat tgtcagcttt atattacctg gatatggaag gaaactattt 2250

ttattctgca tgttcttcct aagcgtcatc ttgagccttg cacatgatac tcagattcct 2310

caccttgct taggagtaaa acataataca ctttacaggg tgatatctcc atagttattt 2370

gaagtggctt ggaaaaagca agattaactt ctgacattgg ataaaaatca acaaatcagc 2430

cctagagtta ttcaaatggt aattgacaaa aactaaaata tttcccttcg agaaggagtg 2490

gaatgtggtt tggcagaaca actgcatttc acagcttttc cggttaaatt ggagcactaa 2550

acgtttagat gcataccaaa ttatgcatgg gcccttaata taaaaggctg gctaccagct 2610

ttgacacagc actattcatc ctctggccaa acaactgtgg ttaaacaaca catgtaaatt 2670

gctttttaac agctgatact ataataagac aaagccaaaa tgcaaaaatt gggctttgat 2730

tggcactttt tgaaaaatat gcaacaaata tgggatgtaa tctggatggc cgcttctgta 2790

cttaatgtga agtatttaga tacctttttg aacacttaac agtttcttct gacaatgact 2850

tttgtaagga ttggtactat ctatcattcc ttataatgta cattgtctgt cactaatcct 2910

cagatcttgc tgtattgtca cctaaattgg tacaggtact gatgaaaata tctaatggat 2970

aatcataaca ctcttggtca catgtttttc ctgcagcctg aaggttttta aaagaaaaag 3030

atatcaaatg cctgctgcta ccacccttt aaattgctat cttttgaaaa gcaccagtat 3090

gtgttttaga ttgatttccc tattttaggg aaatgacaga cagtagtttc agttctgatg 3150

gtataagcaa aacaaataaa acatgtttat aaaagttgta tcttgaaaca ctggtgttca 3210

acagctagca gcttatgtgg ttcaccccat gcattgttag tgtttcagat tttatggtta 3270

tctccagcag ctgtttctgt agtacttgca tttatc 3306

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<212> PRT
<213> Canis familiaris

<400> 12

Met Pro Ser Ala Thr Ser Leu 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 Ala Ala
20 25 30

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

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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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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
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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
        675


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<212>  DNA
<213>  Canis familiaris


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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

ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag        144
Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln
        35                  40                  45

cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag        192
His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln
    50                  55                  60

atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag        240
Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys
65                  70                  75                  80

ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt        288
Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu
                85                  90                  95
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aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat        336
Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn
            100                 105                 110

aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt        384
Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser
        115                 120                 125

caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt        432
Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu
    130                 135                 140

atg aga gag gaa gcg gaa caa aaa cgt tta aaa act gta ctt gag ctc        480
Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu
145                 150                 155                 160

cag tat gtt ttg gac aaa ttg gga gat gat gaa gtg aga act gac ctg        528
Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu
                165                 170                 175

aag caa ggt ttg aat gga gtg cca ata ttg tct gaa gaa gaa ttg tcg        576
Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser
            180                 185                 190

ttg ttg gat gaa ttc tac aaa tta gca gac cct gaa cgg gac atg agc        624
Leu Leu Asp Glu Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser
        195                 200                 205

ttg agg ttg aat gag cag tat gaa cat gct tcc att cac ctg tgg gac        672
Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp
    210                 215                 220

ttg ctg gaa gga aag gaa aag tct gta tgt gga aca acc tat aaa gca        720
Leu Leu Glu Gly Lys Glu Lys Ser Val Cys Gly Thr Thr Tyr Lys Ala
225                 230                 235                 240

cta aag gaa att gtt gag cgt gtt ttc cag tca aat tac ttt gac agc        768
Leu Lys Glu Ile Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser
                245                 250                 255

act cac aac cac cag aat ggg cta tgt gag gaa gaa gag gca gcc tca        816
Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser
            260                 265                 270

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 ggt gaa aag gag cag        960
Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln
305                 310                 315                 320

gta gat gag tgg acg gtc gaa aca gtg gag gtg gtg aat tca ctc cag       1008
Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln
                325                 330                 335

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
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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
                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
            420                 425                 430

gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag       1344
Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu
        435                 440                 445

ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag       1392
Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu
    450                 455                 460

caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct       1440
Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser
465                 470                 475                 480

tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct       1488
Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser
                485                 490                 495

cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt       1536
Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser
            500                 505                 510

gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc       1584
Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe
        515                 520                 525

aat atg aat gcc cca gtt cct cct gtt aat gaa cca gaa act ttg aaa       1632
Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys
    530                 535                 540

caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag       1680
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
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    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

tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag       2064
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
    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 ggccagtgta ccataatatg     2214

ttaccagaag agttattatc tatttggact gttttcatcc cataaagaca ggactacaat     2274

tgtcagc                                                              2281


<210>  14
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<212>  PRT
<213>  Canis familiaris

<400>  14

Met Pro Ser Ala Thr Ser Leu 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 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
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
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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
            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
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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 Arg Gly Gly Pro Pro Arg Pro
    690                 695                 700


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


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<213>  Bos taurus


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<222>  (82)..(2208)

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ctctcccctt acggtttcaa g atg cct tcg gcc acc agc cac agc gga agc        111
                       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
            30                  35                  40

ggc acc ggg gct gtc cag acc gag gcc atg aag cag att ctc ggg gtg        255
Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val
        45                  50                  55

atc gac aag aaa ctt cgg aac ctg gag aag aaa aag ggc aag ctt gat        303
Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp
    60                  65                  70

gat tat cag gaa cga atg aac aaa ggg gaa agg ctt aat caa gat cag        351
Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln
75                  80                  85                  90

ctg gat gcc gtg tct aag tac cag gaa gtc aca aat aac ttg gag ttt        399
Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe
                95                  100                 105
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gca aaa gaa tta cag agg agt ttc atg gca tta agc caa gat att cag        447
Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln
            110                 115                 120

aaa aca ata aag aag aca gca cgt cgg gag cag ctt atg aga gag gaa        495
Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu
        125                 130                 135

gct gaa cag aaa cgt tta aaa aca gta ctt gag ctg cag tat gtt ttg        543
Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu
    140                 145                 150

gac aaa cta gga gat gat gaa gtg aga act gac ctg aag caa ggt ttg        591
Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp Leu Lys Gln Gly Leu
155                 160                 165                 170

aat gga gtg cca ata ttg tct gaa gag gag ttg tcg ttg tta gat gag        639
Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu
                175                 180                 185

ttc tac aaa tta gca gac cct gaa cga gac atg agc ttg agg ttg aat        687
Phe Tyr Lys Leu Ala Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn
            190                 195                 200

gag cag tat gaa cat gcc tcc att cac ctg tgg gac ttg ctg gaa gga        735
Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly
        205                 210                 215

aag gaa aaa cct gta tgt gga aca act tat aaa gct cta aag gaa att        783
Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile
    220                 225                 230

gtt gag cgt gtt ttc cag tca aac tac ttt gac agc acc cac aac cac        831
Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His
235                 240                 245                 250

cag aat ggt ctg tgt gag gaa gag gag gca gcc tca gca cct aca gtt        879
Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val
                255                 260                 265

gaa gac cag gca gct gaa gct gaa cct gag cca gtg gaa gaa tat act        927
Glu Asp Gln Ala Ala Glu Ala Glu Pro Glu Pro Val Glu Glu Tyr Thr
            270                 275                 280

gaa caa aat gag gtt gaa tca aca gag tat gta aat aga caa ttt atg        975
Glu Gln Asn Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met
        285                 290                 295

gca gaa aca cag ttc agc agt ggt gaa aag gag cag gta gat gat tgg       1023
Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Asp Trp
    300                 305                 310

aca gtt gaa aca gtt gag gtg gta aat tca ctc cag cag caa cct cag       1071
Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln
315                 320                 325                 330

gct gca tct cct tca gta cca gaa ccc cac tct ttg acc cca gtg gct       1119
Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala
                335                 340                 345

caa gcc gat ccc ctc gtg aga aga cag cga gta cag gac ctt atg gca       1167
Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala
            350                 355                 360
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caa atg cag ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt       1215
Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe
        365                 370                 375

gaa aac cag aca ctt gat cct gcc att gta tct gca cag ccg atg aat       1263
Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn
    380                 385                 390

cca gca cag aac atg gac ata ccc cag ctg gtt tgc cct cca gtt cat       1311
Pro Ala Gln Asn Met Asp Ile Pro Gln Leu Val Cys Pro Pro Val His
395                 400                 405                 410

tct gaa tct aga ctt gct caa cct aat caa gtt tct gta cag cca gaa       1359
Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Ser Val Gln Pro Glu
                415                 420                 425

gct aca cag gtt cct ttg gtt tca tcc aca agt gag gga tat aca gca       1407
Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala
            430                 435                 440

tct caa ccc ttg tac caa cct tct cat gct act gac caa cga cca caa       1455
Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Asp Gln Arg Pro Gln
        445                 450                 455

aag gaa ccg att gat cag att cag gcg acg atc tct tta aat aca gac       1503
Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp
    460                 465                 470

cag act aca gca tca tca tcc ctt cct gct gct tct cag cct caa gtg       1551
Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val
475                 480                 485                 490

ttc cag gct ggg aca agc aaa cct tta cat agc agt gga atc aat gta       1599
Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val
                495                 500                 505

aat gca gct cca ttc caa tcc atg caa acg gta ttc aat atg aat gcc       1647
Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala
            510                 515                 520

cca gtt cct cct gtt aat gaa cca gaa act tta aaa cag caa aat cag       1695
Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln
        525                 530                 535

tac cag gcc agt tac aac cag agc ttt tcc agt cag cct cac caa gta       1743
Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val
    540                 545                 550

gaa caa aca gag ctt cag caa gaa cag ctt caa aca gtg gtt ggc act       1791
Glu Gln Thr Glu Leu Gln Gln Glu Gln Leu Gln Thr Val Val Gly Thr
555                 560                 565                 570

tat cat ggt tct cag gac cag ccc cat caa gtg act ggt aac cac cag       1839
Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr Gly Asn His Gln
                575                 580                 585

cag cct cct cag cag aac act gga ttt cca cgt agc aat cag ccc tat       1887
Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Asn Gln Pro Tyr
            590                 595                 600

tac aac agt cgt ggt gtg tct cgt gga ggt tcc cgt ggt gct aga ggc       1935
Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly
        605                 610                 615

ttg atg aat gga tac aga gga cct gct aat gga ttc aga gga gga tat       1983
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Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr
    620                 625                 630

gat ggt tac cgc cct tca ttc tct act aac act cca aac agt ggt tat       2031
Asp Gly Tyr Arg Pro Ser Phe Ser Thr Asn Thr Pro Asn Ser Gly Tyr
635                 640                 645                 650

aca caa tct caa ttc agt gct ccc cgg gac tac tct ggc tat cag cgg       2079
Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg
                655                 660                 665

gat gga tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca       2127
Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro
            670                 675                 680

cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg       2175
Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly
        685                 690                 695

atg ccg caa atg aac act cag caa gtg aat taa tctgattcac aggattatgt     2228
Met Pro Gln Met Asn Thr Gln Gln Val Asn
    700                 705

ttaatcgcca aaaacacact ggccagtgta ccataatatg ttaccagaag agttattatc     2288

tatttgttct ccctttcagg aaacttattg taaagggact gttttcatcc cataaagaca     2348

ggactacaat tgtcagcttt atattacctg gatatggaag gaaactattt ttactctgca     2408

tgttctgtcc taagcgtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc     2468

ttaggagtaa aacataatat actttaatgg ggtgatatct ccatagttat ttgaagtggc     2528

ttggataaag caagactgac ttctgacatt ggataaaatc tacaaatcag ccctagagtc     2588

attcagtggt aactgacaaa actaaaatat ttcccttgaa aggaagatgg aaggagtgga     2648

gtgtggtttg gcagaacaac tgcatttcac agcttttcca cttaaattgg agcactgaac     2708

atttagatgc ataccgaatt atgcatgggc cctaatcaca cagacaaggc tggtgccagc     2768

cttaggcttg acacggcagt gttcaccctc tggccagacg actgtggttc aagacacatg     2828

taaattgctt tttaacagct gatactgtat aagacaaagc caaaatgcaa aattaggctt     2888

tgattggcac ttttcgaaaa atatgcaaca attaagggat ataatctgga tggccgcttc     2948

tgtacttaat gtgaaatatt tagatacctt tcaaacactt aacagtttct ttgacaatga     3008

gttttgtaag gattggtagt aaatatcatt ccttatgacg tacattgtct gtcactaatc     3068

cttggatctt gctgtattgt cacctaaatt ggtacaggta ctgatgaaaa tctaatggat     3128

aatcataaca ctcttggtta catgtttttc ctgcagcctg aaagttttta taagaaaaag     3188

acatcaaatg cctgctgctg ccacccttttt aaattgctat cttttgaaaa gcaccagtat     3248

gtgttttaga ttgatttccc tattttaggg aaatgacagt cagtagtttc acttctgatg     3308

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aaaaaaaaaa aaaaaaaa                                                  3386
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<213> Bos taurus

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1               5                   10                  15


Pro Pro Pro Pro Ser Gly Ser Ser Gly Asn Glu Ala Gly Ala Gly Ala
            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
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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
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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

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<222> (1)..(1917)

<400> 17

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Met Glu Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu
1               5                   10                  15

agg ctt aat cag gat cag ctg gat gct gtg tct aag tac cag gaa gtc         96
Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val
            20                  25                  30

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
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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       1296
Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser
            420                 425                 430

agt ggg atc aat gta aat gca gcg cca ttc cag tcc atg caa acg gtg       1344
Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val
        435                 440                 445

ttc aac atg aat gcc ccg gtt cct cct gtt aat gaa cca gaa act tta       1392
Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu
    450                 455                 460

aaa cag caa aat cag tac cag gcc agc tat aac cag agc ttt tcc agt       1440
Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser
465                 470                 475                 480

ccg cct cac caa gta gag cag aca gag ctt ccg caa gag cag ctt cag       1488
Pro Pro His Gln Val Glu Gln Thr Glu Leu Pro Gln Glu Gln Leu Gln
                485                 490                 495

acg gtg gtt ggt act tac cat gct tcc caa gac cag ccc cat caa gtg       1536
Thr Val Val Gly Thr Tyr His Ala Ser Gln Asp Gln Pro His Gln Val
            500                 505                 510
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acc ggt aac cac cag cag cct ccc cag cag aac act ggg ttt cca cgt       1584
Thr Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
        515                 520                 525

agc agt cag ccc tat tac aac agt cgt ggt gtg tct cgt gga ggc tcc       1632
Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
    530                 535                 540

cgt ggt gct aga ggc ttg atg aat gga tac agg ggc cct gcc aat gga       1680
Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
545                 550                 555                 560

ttc aga gga gga tat gat ggt tac cgc cct tcg ttc tct aac act cca       1728
Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
                565                 570                 575

aac agc ggt tac aca cag tct cag ttc agt gct ccc cgg gac tac tct       1776
Asn Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser
            580                 585                 590

ggc tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg       1824
Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
        595                 600                 605

cag agt gga ccc cgg gga gcc cca cga ggt cgt gga ggg ccc cca aga       1872
Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
    610                 615                 620

ccc aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa           1917
Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
625                 630                 635

tctgattcac aggattatct ttaatcgcca aaacacactg gccagtgtac cataatatgt     1977

taccagaaga gttattatct atttgttctc cctttcagga aacttattgt aaagggactg     2037

ttttcatccc ataaagacag gactacagtt gtcagcttta tattacctgg atatggaagg     2097

aaactatttt tactctgcat gttctgtcct aagcgtcatc ttgagccttg cacatgatac     2157

tcagattcct ttcccttgct taggagtaaa acataatata ctttatgggg tgataatatc     2217

tccatagtta tttgaagtgg cttggaaaaa gcaagattga cttttgacat tggataaaat     2277

ctacaaatca gccctagagt ttcatggtca ttcacaaaac taaaatattt cccttgaaag     2337

gaagatggaa ggactggagt gtggtttggc agaacaactg catttcacag cttttcctat     2397

taaattggag cactgaatgt taaatgcata ccaaattatg catgggccct taatcacaca     2457

tacatggcta ccagctttga cacagcacta ttcatcctct ggccaaacga ctgtggttaa     2517

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tctctcatgg ataaacctaa cactcttcgt cacatgtttt tcctgcagcc tgaaggtttt     2877

taaaaggaaa agatatcaaa tgcctgctgc taccaccctt ttaaattgct atcttttgaa     2937
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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
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Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala
180 185 190

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

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                 320

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                 400

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
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450 455 460

Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser
465 470 475 480

Pro Pro His Gln Val Glu Gln Thr Glu Leu Pro Gln Glu Gln Leu Gln
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
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Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
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cggggacagg gcgaagcggc ctgcgcccac ggagcgcacg tctctgttct caacgcagca 120

ccacccttgc ccccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg 178

atg ccc tcg gcc acc agc cac agc gga agc ggc agc aaa tcg tcg gga 226

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

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

gat gtg aga aca gat ctg aaa caa ggt ttg agt gga gtg cca ata ttg        706
Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

tct gag gag gag ttg tca ttg ctg gat gag ttc tac aag ctc gta gat        754
Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

cct gag cgt gac atg agt tta agg tta aat gag cag tat gaa cat gcc        802
Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

tca att cac ttg tgg gat ttg ctg gaa ggg aaa gaa aag cct gtg tgt        850
Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

gga aca acc tat aaa gct cta aag gaa att gtt gag cgt gtt ttc cag        898
Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

tca aac tac ttt gat agc act cac aat cat caa aat ggg ttg tgt gag        946
Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

gag gaa gag gcg gct tca gcg ccc aca gtg gag gac cag gta gct gaa        994
Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
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            260                 265                 270

gct gaa cct gag cca gcg gaa gaa tac aca gag caa agt gag gtt gaa       1042
Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

tca aca gag tat gtc aat agg cag ttc atg gca gaa aca cag ttc agc       1090
Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

agt ggt gag aag gag caa gtg gat gag tgg aca gtt gaa aca gtt gag       1138
Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

gtt gta aac tca ctc cag cag caa cct cag gct gcg tcc cct tca gtc       1186
Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

cca gag ccc cac tct ttg act cca gtg gct cag tca gat cca ctt gtg       1234
Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln Ser Asp Pro Leu Val
            340                 345                 350

aga agg cag cgt gta caa gat ctt atg gca caa atg caa ggg ccc tat       1282
Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

aat ttc ata cag gat tca atg ttg gat ttt gaa aat cag acg ctt gat       1330
Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380

cct gcc att gta tcc gca cag cct atg aac cct acc cag aac atg gat       1378
Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

atg cct cag ctg gtt tgc cct cag gtt cat tct gaa tct aga ctt gcc       1426
Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

caa tct aat caa gtt cct gta caa cca gaa gcc aca cag gtt cct ttg       1474
Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

gtt tca tcc aca agt gag ggg tat aca gca tct cag ccc ttg tac cag       1522
Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

cca tct cat gct acg gag cag cgg ccg cag aaa gag cca atg gat cag       1570
Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
    450                 455                 460

att cag gca aca ata tct ttg aat aca gac cag act aca gca tcc tca       1618
Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

tcc ctt cct gct gct tct cag cct caa gtg ttc cag gct ggg aca agt       1666
Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

aaa cct ttg cac agc agt gga atc aat gta aat gca gct cca ttc cag       1714
Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

tcc atg caa acg gtg ttc aat atg aat gct cca gtc cct cct gct aat       1762
Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525
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gaa cca gaa acg tta aaa caa cag agt cag tac cag gcc act tat aac       1810
Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540

cag agt ttt tcc agt cag cct cac caa gtg gaa caa aca gag ctt caa       1858
Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560

caa gac caa ctg caa acg gtg gtt ggc act tac cat gga tcc cag gac       1906
Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

cag cct cat caa gtg cct ggt aac cac cag caa ccc cca cag cag aac       1954
Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

act ggc ttt cca cgt agc agt cag cct tat tac aac agt cgt ggg gta       2002
Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605

tct cga gga ggg tct cgt ggt gcc aga ggc ttg atg aat gga tac agg       2050
Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

ggc cct gcc aat gga ttt aga gga gga tat gat ggt tac cgc cct tca       2098
Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640

ttc tcg aac act cca aac agt ggt tat tca cag tct cag ttc act gct       2146
Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655

ccc cgg gac tac tct ggt tac cag cgg gat gga tat cag cag aat ttc       2194
Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

aag cga ggc tct ggg cag agt gga cca cgg gga gcc cca cga ggt cgt       2242
Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg
        675                 680                 685

gga ggg ccc cca aga ccc aac aga ggg atg ccg caa atg aac act cag       2290
Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln
    690                 695                 700

caa gtg aat taa tgtgatacac aggattatgt ttaatcgcca aaaacacact           2342
Gln Val Asn
705

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

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

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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
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

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
                245                 250                 255

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
        275                 280                 285

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

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

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 Thr Gln Asn Met Asp
385                 390                 395                 400

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

Gln Ser Asn Gln Val Pro 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 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
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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 Arg
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Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln
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Gln Val Asn
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tctcttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc        171
                    Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly
                    1               5                   10

agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag        219
Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu
            15                  20                  25

gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc        267
Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly
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acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc        315
Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile
    45                  50                  55

gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat        363
Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
60                  65                  70                  75

tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg        411
Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
                80                  85                  90

gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca        459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
            95                  100                 105

aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa        507
Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
        110                 115                 120

aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca        555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
    125                 130                 135

gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat        603
Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
140                 145                 150                 155

aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt        651
Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
                160                 165                 170

gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc        699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
            175                 180                 185

tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag        747
Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu
        190                 195                 200

cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa        795
Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys
    205                 210                 215

gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt        843
Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val
220                 225                 230                 235

gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa        891
Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln
                240                 245                 250

aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag        939
Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu
            255                 260                 265

gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag        987
Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu
        270                 275                 280

caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca       1035
Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala
    285                 290                 295
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gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca       1083
Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr
300                 305                 310                 315

gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct       1131
Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala
                320                 325                 330

gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag       1179
Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln
            335                 340                 345

tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa       1227
Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln
        350                 355                 360

atg caa ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt gaa       1275
Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu
    365                 370                 375

aat cag acg ctt gat cct gcc att gta tcc gca cag cct atg aac cct       1323
Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro
380                 385                 390                 395

acc cag aac atg gat atg cct cag ctg gtt tgc cct cag gtt cat tct       1371
Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val His Ser
                400                 405                 410

gaa tct aga ctt gcc caa tct aat caa gtt cct gta caa cca gaa gcc       1419
Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala
            415                 420                 425

aca cag gtt cct ttg gtt tca tcc aca agt gag ggg tat aca gca tct       1467
Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser
        430                 435                 440

cag ccc ttg tac cag cca tct cat gct acg gag cag cgg ccg cag aaa       1515
Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys
    445                 450                 455

gag cca atg gat cag att cag gca aca ata tct ttg aat aca gac cag       1563
Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln
460                 465                 470                 475

act aca gca tcc tca tcc ctt cct gct gct tct cag cct caa gtg ttc       1611
Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe
                480                 485                 490

cag gct ggg aca agt aaa cct ttg cac agc agt gga atc aat gta aat       1659
Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn
            495                 500                 505

gca gct cca ttc cag tcc atg caa acg gtg ttc aat atg aat gct cca       1707
Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro
        510                 515                 520

gtc cct cct gct aat gaa cca gaa acg tta aaa caa cag agt cag tac       1755
Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr
    525                 530                 535

cag gcc act tat aac cag agt ttt tcc agt cag cct cac caa gtg gaa       1803
Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu
540                 545                 550                 555
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caa aca gag ctt caa caa gac caa ctg caa acg gtg gtt ggc act tac       1851
Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr
                560                 565                 570

cat gga tcc cag gac cag cct cat caa gtg cct ggt aac cac cag caa       1899
His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln
            575                 580                 585

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

atg aat gga tac agg ggc cct gcc aat gga ttt aga gga gga tat gat       2043
Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp
620                 625                 630                 635

ggt tac cgc cct tca ttc tcg aac act cca aac agt ggt tat tca cag       2091
Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln
                640                 645                 650

tct cag ttc act gct ccc cgg gac tac tct ggt tac cag cgg gat gga       2139
Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly
            655                 660                 665

tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga       2187
Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly
        670                 675                 680

gcc cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg       2235
Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro
    685                 690                 695

caa atg aac act cag caa gtg aat taa tgtgatacac aggattatgt             2282
Gln Met Asn Thr Gln Gln Val Asn
700                 705

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35 40 45

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
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

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
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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
275 280 285

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
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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
385                 390                 395                 400

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

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

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
    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
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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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    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
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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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Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln
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Gln Val Asn
705


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

agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag        219
Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu
            15                  20                  25

gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc        267
Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly
        30                  35                  40

acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc        315
Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile
    45                  50                  55

gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat        363
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Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
60                  65                  70                  75

tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg        411
Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
                80                  85                  90

gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca        459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
            95                  100                 105

aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa        507
Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
        110                 115                 120

aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca        555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
    125                 130                 135

gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat        603
Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
140                 145                 150                 155

aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt        651
Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
                160                 165                 170

gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc        699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
            175                 180                 185

tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag        747
Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu
        190                 195                 200

cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa        795
Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys
    205                 210                 215

gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt        843
Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val
220                 225                 230                 235

gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa        891
Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln
                240                 245                 250

aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag        939
Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu
            255                 260                 265

gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag        987
Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu
        270                 275                 280

caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca       1035
Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala
    285                 290                 295

gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca       1083
Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr
300                 305                 310                 315

gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct       1131
Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala
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                320                 325                 330

gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag       1179
Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln
            335                 340                 345

tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa       1227
Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln
        350                 355                 360

atg caa ggg ccc tat aat ttc ata cag acg ctt gat cct gcc att gta       1275
Met Gln Gly Pro Tyr Asn Phe Ile Gln Thr Leu Asp Pro Ala Ile Val
    365                 370                 375

tcc gca cag cct atg aac cct acc cag aac atg gat atg cct cag ctg       1323
Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu
380                 385                 390                 395

gtt tgc cct cag gtt cat tct gaa tct aga ctt gcc caa tct aat caa       1371
Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala Gln Ser Asn Gln
                400                 405                 410

gtt cct gta caa cca gaa gcc aca cag gtt cct ttg gtt tca tcc aca       1419
Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr
            415                 420                 425

agt gag ggg tat aca gca tct cag ccc ttg tac cag cca tct cat gct       1467
Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala
        430                 435                 440

acg gag cag cgg ccg cag aaa gag cca atg gat cag att cag gca aca       1515
Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln Ile Gln Ala Thr
    445                 450                 455

ata tct ttg aat aca gac cag act aca gca tcc tca tcc ctt cct gct       1563
Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala
460                 465                 470                 475

gct tct cag cct caa gtg ttc cag gct ggg aca agt aaa cct ttg cac       1611
Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His
                480                 485                 490

agc agt gga atc aat gta aat gca gct cca ttc cag tcc atg caa acg       1659
Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr
            495                 500                 505

gtg ttc aat atg aat gct cca gtc cct cct gct aat gaa cca gaa acg       1707
Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn Glu Pro Glu Thr
        510                 515                 520

tta aaa caa cag agt cag tac cag gcc act tat aac cag agt ttt tcc       1755
Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn Gln Ser Phe Ser
    525                 530                 535

agt cag cct cac caa gtg gaa caa aca gag ctt caa caa gac caa ctg       1803
Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln Gln Asp Gln Leu
540                 545                 550                 555

caa acg gtg gtt ggc act tac cat gga tcc cag gac cag cct cat caa       1851
Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln
                560                 565                 570

gtg cct ggt aac cac cag caa ccc cca cag cag aac act ggc ttt cca       1899
Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro
            575                 580                 585
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cgt agc agt cag cct tat tac aac agt cgt ggg gta tct cga gga ggg       1947
Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly
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tct cgt ggt gcc aga ggc ttg atg aat gga tac agg ggc cct gcc aat       1995
Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn
    605                 610                 615

gga ttt aga gga gga tat gat ggt tac cgc cct tca ttc tcg aac act       2043
Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr
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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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tct ggt tac cag cgg gat gga tat cag cag aat ttc aag cga ggc tct       2139
Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser
            655                 660                 665

ggg cag agt gga cca cgg gga gcc cca cga ggt cgt gga ggg ccc cca       2187
Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro
        670                 675                 680

aga ccc aac aga ggg atg ccg caa atg aac act cag caa gtg aat taa       2235
Arg Pro Asn Arg Gly Met Pro Gln Met Asn Thr Gln Gln Val Asn
    685                 690                 695

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gaaactattt ttattctgca tgttctgtcc taagcgtcat cttgagcctt gcacacaata     2475

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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
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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

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Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr
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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
                245                 250                 255


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
        275                 280                 285


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
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 Ser Asp Pro Leu Val
            340                 345                 350


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


Asn Phe Ile Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met
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370 375 380

Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val
385 390 395 400

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

Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr
420 425 430

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
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Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn
500 505 510

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
530 535 540

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
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Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser Ser Gln Pro
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Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg Gly Ala Arg
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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

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Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro
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Met Pro Gln Met Asn Thr Gln Gln Val Asn
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ccacccttgc ccccctcggc tgcccactcc agacgtccag cggctccgcg cgcgcacg        178

atg ccc tcg gcc acc agc cac agc gga agc ggc agc aaa tcg tcg gga        226
Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly Ser Lys Ser Ser Gly
1               5                   10                  15

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
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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

gat gtg aga aca gat ctg aaa caa ggt ttg agt gga gtg cca ata ttg        706
Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser Gly Val Pro Ile Leu
                165                 170                 175

tct gag gag gag ttg tca ttg ctg gat gag ttc tac aag ctc gta gat        754
Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp
            180                 185                 190

cct gag cgt gac atg agt tta agg tta aat gag cag tat gaa cat gcc        802
Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala
        195                 200                 205

tca att cac ttg tgg gat ttg ctg gaa ggg aaa gaa aag cct gtg tgt        850
Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys
    210                 215                 220

gga aca acc tat aaa gct cta aag gaa att gtt gag cgt gtt ttc cag        898
Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val Glu Arg Val Phe Gln
225                 230                 235                 240

tca aac tac ttt gat agc act cac aat cat caa aat ggg ttg tgt gag        946
Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln Asn Gly Leu Cys Glu
                245                 250                 255

gag gaa gag gcg gct tca gcg ccc aca gtg gag gac cag gta gct gaa        994
Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu Asp Gln Val Ala Glu
            260                 265                 270

gct gaa cct gag cca gcg gaa gaa tac aca gag caa agt gag gtt gaa       1042
Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu
        275                 280                 285

tca aca gag tat gtc aat agg cag ttc atg gca gaa aca cag ttc agc       1090
Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser
    290                 295                 300

agt ggt gag aag gag caa gtg gat gag tgg aca gtt gaa aca gtt gag       1138
Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

gtt gta aac tca ctc cag cag caa cct cag gct gcg tcc cct tca gtc       1186
Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala Ala Ser Pro Ser Val
                325                 330                 335

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

aga agg cag cgt gta caa gat ctt atg gca caa atg caa ggg ccc tat       1282
Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr
        355                 360                 365

aat ttc ata cag gat tca atg ttg gat ttt gaa aat cag acg ctt gat       1330
Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn Gln Thr Leu Asp
    370                 375                 380
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cct gcc att gta tcc gca cag cct atg aac cct acc cag aac atg gat       1378
Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro Thr Gln Asn Met Asp
385                 390                 395                 400

atg cct cag ctg gtt tgc cct cag gtt cat tct gaa tct aga ctt gcc       1426
Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415

caa tct aat caa gtt cct gta caa cca gaa gcc aca cag gtt cct ttg       1474
Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu
            420                 425                 430

gtt tca tcc aca agt gag ggg tat aca gca tct cag ccc ttg tac cag       1522
Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln
        435                 440                 445

cca tct cat gct acg gag cag cgg ccg cag aaa gag cca atg gat cag       1570
Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys Glu Pro Met Asp Gln
    450                 455                 460

att cag gca aca ata tct ttg aat aca gac cag act aca gca tcc tca       1618
Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser
465                 470                 475                 480

tcc ctt cct gct gct tct cag cct caa gtg ttc cag gct ggg aca agt       1666
Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe Gln Ala Gly Thr Ser
                485                 490                 495

aaa cct ttg cac agc agt gga atc aat gta aat gca gct cca ttc cag       1714
Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
            500                 505                 510

tcc atg caa acg gtg ttc aat atg aat gct cca gtc cct cct gct aat       1762
Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro Val Pro Pro Ala Asn
        515                 520                 525

gaa cca gaa acg tta aaa caa cag agt cag tac cag gcc act tat aac       1810
Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
    530                 535                 540

cag agt ttt tcc agt cag cct cac caa gtg gaa caa aca gag ctt caa       1858
Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
545                 550                 555                 560

caa gac caa ctg caa acg gtg gtt ggc act tac cat gga tcc cag gac       1906
Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr His Gly Ser Gln Asp
                565                 570                 575

cag cct cat caa gtg cct ggt aac cac cag caa ccc cca cag cag aac       1954
Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
            580                 585                 590

act ggc ttt cca cgt agc agt cag cct tat tac aac agt cgt ggg gta       2002
Thr Gly Phe Pro Arg Ser Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val
        595                 600                 605

tct cga gga ggg tct cgt ggt gcc aga ggc ttg atg aat gga tac agg       2050
Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg
    610                 615                 620

ggc cct gcc aat gga ttt aga gga gga tat gat ggt tac cgc cct tca       2098
Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser
625                 630                 635                 640
```

```
ttc tcg aac act cca aac agt ggt tat tca cag tct cag ttc act gct       2146
Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln Ser Gln Phe Thr Ala
                645                 650                 655

ccc cgg gac tac tct ggt tac cag cgg gat gga tat cag cag aat ttc       2194
Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe
            660                 665                 670

aag cga ggc tct ggg cag agt gga cca cgg gga gcc cca cga ggt aat       2242
Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Asn
        675                 680                 685

ata ttg tgg tgg tga tcctagctcc tatgtggagc ttctgttctg gccttggaag       2297
Ile Leu Trp Trp
    690

aactgttcat agtccgcatg taggttacat gttaggaata catttatctt ttccagactt     2357

gttgctaaag attaaatgaa atgctctgtt tctaaaattt catcttgaat ccaaatttta     2417

atttttgaat gactttccct gctgttgtct tcaaaatcag aacattttct ctgcctcaga     2477

aaagcgtttt tccaactgga aatttatttt tcaggtctta aaacctgcta aatgttttta     2537

ggaagtacct actgaaactt tttgtaagac atttttggaa cgagcttgaa catttatata     2597

aatttattac cctctttgat ttttgaaaca tgcatattat atttaggctg agaagccctt     2657

caaatggcca gataagccac agttttagct agagaaccat ttagaattga cataactaat     2717

ctaaacttga acacttttag gaccaatgtt agtgttctaa ataccaacat atttctgatg     2777

tttaaacaga tctcccaaat tcttaggacc ttgatgtcat taaaatttag aatgacaagc     2837

ttaagaggct ttagtttcat ttgtttttca agtaatgaaa aataatttct tacatgggca     2897

gatagttaat ttgttgaaca attacaggta gcatttcatg taatctgatg ttctaaatgg     2957

ttctcttatt gaaggaggtt aaagaattag gtttcttaca gtttttggct ggccatgaca     3017

tgtataaaat gtatattaag gaggaattat aaagtacttt aatttgaatg ctagtggcaa     3077

ttgatcatta agaaagtact ttaaagcaaa aggttaatgg gtcatctggg aaaaatactg     3137

aagtatcaaa ggtatttgca tgtgaatgtg ggttatgttc ttctatccca ccttgtagca     3197

tattctatga aagttgagtt aaatgatagc taaaatatct gtttcaacag catgtaaaaa     3257

gttattttaa ctgttacaag tcattataca attttgaatg ttctgtagtt tctttttaac     3317

agtttaggta caaaggtctg ttttcattct ggtgcttttt attaattttg atagtatgat     3377

gtcacttcct attgaaatgt aagctagcgt gtaccttaga atgtgagctc catgagagca     3437

ggtaccttgt ttgtcttcac tgctgtatct attcccaacg cctcatgaca gtgcctggca     3497

catagtaggc actcaataaa tacttgttga atgaatgaaa aaaaaaaaaa a              3548
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Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Gly Ala
            20                  25                  30

Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly Thr Gly Ala Val Gln
        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

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
                245                 250                 255
```

```
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
        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 Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

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

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

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

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 Thr Gln Asn Met Asp
385                 390                 395                 400

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

Gln Ser Asn Gln Val Pro 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 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
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```
        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


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<213>  Mus musculus


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<222>  (139)..(2217)

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tctccccgtc cgtctcctga cttgctggtc ttgtccttcc ctcccgcttt tttcctctcc      120

tctcttctcg gtctaaag atg ccc tcg gcc acc agc cac agc gga agc ggc        171
                  Met Pro Ser Ala Thr Ser His Ser Gly Ser Gly
                  1               5                   10
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agc aaa tcg tcg gga ccg ccg ccg ccg tcc ggt tcc tcc ggg agt gag        219
Ser Lys Ser Ser Gly Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu
            15                  20                  25

gcg gcg gcc ggg gca gct gcg ccg gct tct cag cat ccg gca acc ggc        267
Ala Ala Ala Gly Ala Ala Ala Pro Ala Ser Gln His Pro Ala Thr Gly
        30                  35                  40

acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc        315
Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile
    45                  50                  55

gac aag aaa ctt cgg aac ctg gag aag aaa aag ggt aaa ctt gat gat        363
Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp
60                  65                  70                  75

tac cag gaa cga atg aat aaa ggg gaa agg ctc aat caa gac cag ctg        411
Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu Asn Gln Asp Gln Leu
                80                  85                  90

gat gcc gta tct aag tac cag gaa gtc aca aat aat ttg gag ttt gca        459
Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn Asn Leu Glu Phe Ala
            95                  100                 105

aag gaa tta cag agg agt ttc atg gca tta agt caa gat att cag aaa        507
Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser Gln Asp Ile Gln Lys
        110                 115                 120

aca ata aag aag aca gca cgt cgg gaa cag ctt atg aga gaa gaa gca        555
Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala
    125                 130                 135

gaa cag aag cgc tta aaa act gta ctt gag tta cag tat gta ttg gat        603
Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu Asp
140                 145                 150                 155

aag ctg gga gat gat gat gtg aga aca gat ctg aaa caa ggt ttg agt        651
Lys Leu Gly Asp Asp Asp Val Arg Thr Asp Leu Lys Gln Gly Leu Ser
                160                 165                 170

gga gtg cca ata ttg tct gag gag gag ttg tca ttg ctg gat gag ttc        699
Gly Val Pro Ile Leu Ser Glu Glu Glu Leu Ser Leu Leu Asp Glu Phe
            175                 180                 185

tac aag ctc gta gat cct gag cgt gac atg agt tta agg tta aat gag        747
Tyr Lys Leu Val Asp Pro Glu Arg Asp Met Ser Leu Arg Leu Asn Glu
        190                 195                 200

cag tat gaa cat gcc tca att cac ttg tgg gat ttg ctg gaa ggg aaa        795
Gln Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys
    205                 210                 215

gaa aag cct gtg tgt gga aca acc tat aaa gct cta aag gaa att gtt        843
Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys Ala Leu Lys Glu Ile Val
220                 225                 230                 235

gag cgt gtt ttc cag tca aac tac ttt gat agc act cac aat cat caa        891
Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His Gln
                240                 245                 250

aat ggg ttg tgt gag gag gaa gag gcg gct tca gcg ccc aca gtg gag        939
Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val Glu
            255                 260                 265
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gac cag gta gct gaa gct gaa cct gag cca gcg gaa gaa tac aca gag        987
Asp Gln Val Ala Glu Ala Glu Pro Glu Pro Ala Glu Glu Tyr Thr Glu
        270                 275                 280

caa agt gag gtt gaa tca aca gag tat gtc aat agg cag ttc atg gca       1035
Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met Ala
    285                 290                 295

gaa aca cag ttc agc agt ggt gag aag gag caa gtg gat gag tgg aca       1083
Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Glu Trp Thr
300                 305                 310                 315

gtt gaa aca gtt gag gtt gta aac tca ctc cag cag caa cct cag gct       1131
Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln Ala
                320                 325                 330

gcg tcc cct tca gtc cca gag ccc cac tct ttg act cca gtg gct cag       1179
Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala Gln
            335                 340                 345

tca gat cca ctt gtg aga agg cag cgt gta caa gat ctt atg gca caa       1227
Ser Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala Gln
        350                 355                 360

atg caa ggg ccc tat aat ttc ata cag gat tca atg ttg gat ttt gaa       1275
Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu
    365                 370                 375

aat cag acg ctt gat cct gcc att gta tcc gca cag cct atg aac cct       1323
Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn Pro
380                 385                 390                 395

acc cag aac atg gat atg cct cag ctg gtt tgc cct cag gtt cat tct       1371
Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys Pro Gln Val His Ser
                400                 405                 410

gaa tct aga ctt gcc caa tct aat caa gtt cct gta caa cca gaa gcc       1419
Glu Ser Arg Leu Ala Gln Ser Asn Gln Val Pro Val Gln Pro Glu Ala
            415                 420                 425

aca cag gtt cct ttg gtt tca tcc aca agt gag ggg tat aca gca tct       1467
Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu Gly Tyr Thr Ala Ser
        430                 435                 440

cag ccc ttg tac cag cca tct cat gct acg gag cag cgg ccg cag aaa       1515
Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu Gln Arg Pro Gln Lys
    445                 450                 455

gag cca atg gat cag att cag gca aca ata tct ttg aat aca gac cag       1563
Glu Pro Met Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp Gln
460                 465                 470                 475

act aca gca tcc tca tcc ctt cct gct gct tct cag cct caa gtg ttc       1611
Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val Phe
                480                 485                 490

cag gct ggg aca agt aaa cct ttg cac agc agt gga atc aat gta aat       1659
Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn
            495                 500                 505

gca gct cca ttc cag tcc atg caa acg gtg ttc aat atg aat gct cca       1707
Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe Asn Met Asn Ala Pro
        510                 515                 520

gtc cct cct gct aat gaa cca gaa acg tta aaa caa cag agt cag tac       1755
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Val Pro Pro Ala Asn Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr
    525                 530                 535

cag gcc act tat aac cag agt ttt tcc agt cag cct cac caa gtg gaa       1803
Gln Ala Thr Tyr Asn Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu
540                 545                 550                 555

caa aca gag ctt caa caa gac caa ctg caa acg gtg gtt ggc act tac       1851
Gln Thr Glu Leu Gln Gln Asp Gln Leu Gln Thr Val Val Gly Thr Tyr
                560                 565                 570

cat gga tcc cag gac cag cct cat caa gtg cct ggt aac cac cag caa       1899
His Gly Ser Gln Asp Gln Pro His Gln Val Pro Gly Asn His Gln Gln
            575                 580                 585

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

atg aat gga tac agg ggc cct gcc aat gga ttt aga gga gga tat gat       2043
Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp
620                 625                 630                 635

ggt tac cgc cct tca ttc tcg aac act cca aac agt ggt tat tca cag       2091
Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Ser Gln
                640                 645                 650

tct cag ttc act gct ccc cgg gac tac tct ggt tac cag cgg gat gga       2139
Ser Gln Phe Thr Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly
            655                 660                 665

tat cag cag aat ttc aag cga ggc tct ggg cag agt gga cca cgg gga       2187
Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln Ser Gly Pro Arg Gly
        670                 675                 680

gcc cca cga ggt aat ata ttg tgg tgg tga tcctagctcc tatgtggagc         2237
Ala Pro Arg Gly Asn Ile Leu Trp Trp
    685                 690

ttctgttctg gccttggaag aactgttcat agtccgcatg taggttacat gttaggaata     2297

catttatctt ttccagactt gttgctaaag attaaatgaa atgctctgtt tctaaaattt     2357

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aacattttct ctgcctcaga aaagcgtttt tccaactgga aatttatttt tcaggtctta     2477

aaacctgcta aatgttttta ggaagtacct actgaaactt tttgtaagac atttttggaa     2537

cgagcttgaa catttatata aatttattac cctctttgat ttttgaaaca tgcatattat     2597

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atgtgagctc catgagagca ggtaccttgt ttgtcttcac tgctgtatct attcccaacg 3437

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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
20 25 30

Ala Ala Pro Ala Ser Gln His Pro Ala 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

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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
                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
                245                 250                 255

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
        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 Glu Trp Thr Val Glu Thr Val Glu
305                 310                 315                 320

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

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

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

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 Thr Gln Asn Met Asp
385                 390                 395                 400
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```
Met Pro Gln Leu Val Cys Pro Gln Val His Ser Glu Ser Arg Leu Ala
                405                 410                 415


Gln Ser Asn Gln Val Pro 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 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
```

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            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>
<221>  CDS
<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 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 ggt gac gat gaa gtg cgc agt gac        480
Leu Gln Phe Ile Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Ser Asp
145                 150                 155                 160

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 tcg act gag tat gta        864
Ala Glu Glu Phe Thr Glu Pro Thr Glu Val Glu Ser Thr Glu Tyr Val
        275                 280                 285

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 ggt 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 gag aac cag aca ctt gat cct gcc att gta tct       1152
Ser Met Leu Glu Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser
    370                 375                 380

gca cag ccc atg aat cca gca cag aat ttg gac atg ccg caa atg gtc       1200
Ala Gln Pro Met Asn Pro Ala Gln Asn Leu Asp Met Pro Gln Met Val
385                 390                 395                 400

tgc cct cca gtt cat act gag tca aga ctt gcc cag cct aat caa gtt       1248
Cys Pro Pro Val His Thr Glu Ser Arg Leu Ala Gln Pro Asn Gln Val
                405                 410                 415

cct gtg caa cca gaa gct acg cag gtt ccc ttg gtt tca tct aca agt       1296
Pro Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser
            420                 425                 430
```

```
gag gga tat aca gcc tcc cag ccc atg tat cag cct tct cat acc aca       1344
Glu Gly Tyr Thr Ala Ser Gln Pro Met Tyr Gln Pro Ser His Thr Thr
        435                 440                 445

gag caa cgg cca cag aag gaa tcc att gac cag att cag gct tca atg       1392
Glu Gln Arg Pro Gln Lys Glu Ser Ile Asp Gln Ile Gln Ala Ser Met
    450                 455                 460

tca ctg aat gca gac cag acc ccg tca tca tca tca ctt ccc act gca       1440
Ser Leu Asn Ala Asp Gln Thr Pro Ser Ser Ser Ser Leu Pro Thr Ala
465                 470                 475                 480

tcc cag ccg caa gtt ttc caa gct gga tct agc aaa cct ttg cat agc       1488
Ser Gln Pro Gln Val Phe Gln Ala Gly Ser Ser Lys Pro Leu His Ser
                485                 490                 495

agc gga atc aat gtt aat gca gct cca ttc caa tcc atg caa aca gta       1536
Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val
            500                 505                 510

ttc aac atg aat gca cct gtt cct cct gtt aat gag cca gaa gcc ctt       1584
Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Ala Leu
        515                 520                 525

aag caa caa aat cag tac cag gcc agt tac aac cag agt ttc tcc aat       1632
Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Asn
    530                 535                 540

cag cca cac caa gta gaa caa tca gat ctt cag caa gaa cag ctc cag       1680
Gln Pro His Gln Val Glu Gln Ser Asp Leu Gln Gln Glu Gln Leu Gln
545                 550                 555                 560

aca gtg gtt ggt act tac cat ggt tct ccg gac cag acc cat caa gtg       1728
Thr Val Val Gly Thr Tyr His Gly Ser Pro Asp Gln Thr His Gln Val
                565                 570                 575

gca gga aac cac cag caa cct ccc cag cag aat act gga ttt cca cgc       1776
Ala Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg
            580                 585                 590

aac agt cag cct tat tac aac agt cgg gga gtg tct cgt ggt gga tca       1824
Asn Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser
        595                 600                 605

cgt ggg act cgt gga ttg atg aat ggt tac agg gga cct gca aat gga       1872
Arg Gly Thr Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly
    610                 615                 620

ttt aga gga gga tat gat ggc tac cgt cct tca ttt tcc aac act ccg       1920
Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser Phe Ser Asn Thr Pro
625                 630                 635                 640

aac agt ggt tac acg cag ccc caa ttt aat gct cct cga gat tat tca       1968
Asn Ser Gly Tyr Thr Gln Pro Gln Phe Asn Ala Pro Arg Asp Tyr Ser
                645                 650                 655

aac tac cag cgg gat gga tat cag cag aac ttc aaa cgt ggt tct gga       2016
Asn Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly
            660                 665                 670

caa agt ggg cct cgg gga gct cct cga ggt cgt gga ggg ccc cca aga       2064
Gln Ser Gly Pro Arg Gly Ala Pro Arg Gly Arg Gly Gly Pro Pro Arg
        675                 680                 685

cca aac aga ggg atg cct caa atg aac gct cag caa gtg aat taa           2109
```

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


<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 Ala Thr Ser Pro Pro Val Pro Glu Pro His Thr
                325                 330                 335

Leu Thr Thr Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val
            340                 345                 350

Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Met Gln Asp
        355                 360                 365

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

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

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

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

Glu Gly Tyr Thr Ala Ser Gln Pro Met Tyr Gln Pro Ser His Thr Thr
        435                 440                 445

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

Ser Leu Asn Ala Asp Gln Thr Pro Ser Ser Ser Ser Leu Pro Thr Ala
465                 470                 475                 480
```

```
Ser Gln Pro Gln Val Phe Gln Ala Gly Ser Ser Lys Pro Leu His Ser
                485                 490                 495

Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val
            500                 505                 510

Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Ala Leu
        515                 520                 525

Lys Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Asn
    530                 535                 540

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
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<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
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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

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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
                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
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Gln Gly Thr Leu Val Thr Val Ser Ser
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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
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Gly

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<212> PRT
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<400> 279

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

Gly

<210> 280
<211> 11
<212> PRT
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<400> 280

Arg Ile His Tyr Tyr Tyr Gly Ser Ser Tyr Tyr
1 5 10

<210> 281
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<400> 281

Arg Ala Ser Lys Ser Ile Ser Lys Tyr Leu Ala Trp Tyr Gln Glu
1 5 10 15

<210> 282

<211> 7
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<213> Mus musculus

<400> 282

Ser Gly Ser Thr Leu Gln Ser
1 5

<210> 283
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<400> 283

Gln Gln His Asn Glu Tyr Pro Trp Thr
1 5

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Glu Tyr Ile Ile His
1 5

<210> 285
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Trp Phe Tyr Pro Gly Ser Gly Ser Ile Lys Tyr Asn Glu Lys Phe Lys
1 5 10 15

Asp

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His Glu Val Tyr Tyr Asp Tyr Asp Lys Ser Met
1 5 10

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Leu Tyr Ser Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
1 5 10 15

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Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 289
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Gln Gln Tyr Tyr Ser Tyr Pro Tyr Thr
1 5

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<400> 290

Asn Tyr Leu Ile Glu
1 5

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<400> 291

Val Ile Asn Pro Lys Ser Gly Gly Thr Lys Tyr Asn Glu Lys Phe Arg
1 5 10 15

Gly Lys Ala

<210> 292
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<400> 292

Thr Gly Thr Asp Tyr Trp Gly Gln Gly Thr Thr
1 5 10

<210> 293
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<400> 293

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

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Tyr Thr Ser Ser Leu Arg Ser
1 5

<210> 295
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<400> 295

Gln Gln Tyr Ser Lys Leu Pro Arg Thr
1 5

<210> 296
<211> 12
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<213> Homo sapiens

<400> 296

Phe Thr Ser Gly Glu Lys Glu Gln Val Asp Glu Trp
1 5 10

<210> 297
<211> 16
<212> PRT
<213> Homo sapiens

<400> 297

Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu Leu Gln Tyr Val Leu
1 5 10 15

<210> 298
<211> 16
<212> PRT
<213> Homo sapiens

<400> 298

Val Glu Arg Val Phe Gln Ser Asn Tyr Phe Asp Ser Thr His Asn His
1 5 10 15

<210> 299

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

<400> 299

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

<210> 300
<211> 5
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<213> Mus musculus

<400> 300

Thr Asn Ala Met Asn
1 5

<210> 301
<211> 17
<212> PRT
<213> Mus musculus

<400> 301

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

Val

<210> 302
<211> 11
<212> PRT
<213> Mus musculus

<400> 302

Asp Trp Asp Gly Phe Leu Tyr Phe Asp Tyr Trp
1 5 10

<210> 303
<211> 112
<212> PRT
<213> Mus musculus

<400> 303

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

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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


<210>  304
<211>  15
<212>  PRT
<213>  Mus musculus

<400>  304

Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His Trp Asn Gln Gln
1               5                   10                  15


<210>  305
<211>  7
<212>  PRT
<213>  Mus musculus

<400>  305

Leu Val Ser Asn Leu Glu Ser
1               5


<210>  306
<211>  9
<212>  PRT
<213>  Mus musculus

<400>  306

Gln His Ile Arg Glu Leu Thr Arg Ser
1               5


<210>  307
<211>  104
<212>  PRT
<213>  Mus musculus

<400>  307

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
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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
            100


<210>  308
<211>  14
<212>  PRT
<213>  Homo sapiens

<400>  308

Pro Pro Val Asn Glu Pro Glu Thr Leu Lys Gln Gln Asn Gln
1               5                   10


<210>  309
<211>  12
<212>  PRT
<213>  Homo sapiens

<400>  309

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