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

PHARMAZEUTISCHE ZUSAMMENSETZUNG ZUR BEHANDLUNG UND PRÄVENTION VON
KREBS

COMPOSITION PHARMACEUTIQUE DESTINÉE AU TRAITEMENT ET À LA PRÉVENTION DU
CANCER

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Description

TECHNICAL FIELD

5 **[0001]** The present invention relates to a novel pharmaceutical use of an antibody against CD 179b, as an agent for therapy and/or prophylaxis of cancer.

BACKGROUND ART

10 **[0002]** Cancers are the commonest cause for death among all of the causes for death, and the therapies currently carried out therefor are mainly surgical treatment in combination with radiotherapy and chemotherapy. In spite of the developments of new surgical methods and discovery of new anti-cancer agents in recent years, treatment results of cancers are not improved very much at present except for some cancers. In recent years, by virtue of development in molecular biology and cancer immunology, cancer antigens recognized by antibodies and cytotoxic T cells which are specifically reactive with cancers, as well as the genes encoding the cancer antigens, were identified, and expectations for therapeutic methods specifically targeting cancer antigens have been raised (Non-patent Literature 1).

15 **[0003]** In a therapeutic method for cancer, to reduce side effects, it is desired that the peptide, polypeptide or protein recognized as the antigen exist hardly in normal cells and exist specifically in cancer cells. In 1991, Boon et al. in Ludwig Institute in Belgium isolated a human melanoma antigen MAGE 1 recognized by CD8-positive T cells by a cDNA-expression cloning method using an autologous cancer cell line and cancer-reactive T cells (Non-patent Literature 2). Thereafter, the SEREX (serological identifications of antigens by recombinant expression cloning) method, wherein tumor antigens recognized by antibodies produced in the living body of a cancer patient in response to the cancer of the patient himself are identified by application of a gene expression cloning method, was reported (Non-patent Literature 3; Patent Literature 1), and several cancer antigens which are hardly expressed in normal cells while being specifically expressed in cancer cells have been isolated by this method (Non-patent Literatures 4 to 9). Further, using a part thereof as targets, clinical tests for cell therapies using immunocytes specifically reactive with the cancer antigens, and cancer-specific immunotherapies such as those using vaccines containing the cancer antigens have been carried out.

20 **[0004]** On the other hand, in recent years, various antibody drugs for therapy of cancer have become conspicuous in the world, which drugs target antigen proteins on cancer cells. Since certain levels of pharmacological effects can be obtained with such antibody drugs as cancer-specific therapeutic agents, they are drawing attention, but most of the antigen proteins to be targeted are those also expressed in normal cells, so that, as a result of administration of the antibody, not only cancer cells, but also normal cells expressing the antigen are damaged, resulting in occurrence of side effects, which has been problematic. Thus, it is expected that identification of cancer antigens specifically expressed on the surfaces of cancer cells and employment of antibodies targeting these as drugs will allow therapy with antibody drugs with less side effects.

25 **[0005]** GD179b is known to be a part of the surrogate light chain of immunoglobulin and expressed on the membrane surfaces of precursor cells of B cells (pre-B cells and pro-B cells). It disappears upon differentiation of B cells and is not expressed in mature B cells. However, CD179b is known to be expressed in leukemia (pre-B cell leukemia) cells produced by cancerization of pre-B cells (Non-patent Literatures 10 and 11). Further, CD179b is known to be expressed also in lymphoma (pre-B cell lymphoma) cells produced by cancerization of pre-B cells, and able to be used as a diagnostic marker for pre-B cell lymphoma (Non-patent Literature 12). However, its specific expression has not been reported for leukemia cells other than pre-B cell leukemia cells, lymphomas other than pre-B cell lymphoma, breast cancer cells and the like. Further, there has been no report suggesting that antibodies against CD 179b are useful for therapy and/or prophylaxis of cancer.

PRIOR ART LITERATURES

Patent Literature

30 **[0006]** Patent Literature 1: US 5698396 B

Non-patent Literatures

[0007]

35 Non-patent Literature 1: Tsuyoshi Akiyoshi, "Cancer and Chemotherapy", 1997, Vol. 24, pp. 551-519
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 Non-patent Literature 6: Int. J. Cancer, 29:652-658 (1998)
 Non-patent Literature 7: Int. J. Oncol., 14:703-708 (1999)
 Non-patent Literature 8: Cancer Res., 56:4766-4772 (1996)
 Non-patent Literature 9: Hum. Mol. Genet 6:33-39 (1997)
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 Non-patent Literature 11: Blood, 92:4317-4324 (1998)
 Non-patent Literature 12: Modern Pathology, 17:423-429 (2004)

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0008] The present invention aims to identify cancer antigen proteins specifically expressed on the surfaces of cancer cells and provide uses of antibodies targeting them as agents for therapy and/or prophylaxis of cancer.

MEANS FOR SOLVING THE PROBLEMS

[0009] The present inventors intensively studied to obtain, by the SEREX method using serum from a patient dog from which a canine breast cancer tissue-derived cDNA library was prepared, cDNA encoding a protein which binds to antibodies existing in the serum derived from the cancer-bearing living body, and, based on a human gene homologous to the obtained gene, human CD179b having the amino acid sequence shown in SEQ ID NO:3 was prepared. Further, the present inventors discovered that CD 179b is hardly expressed in normal tissues, but specifically expressed in breast cancer, leukemia and lymphoma cells. Further, the present inventors discovered that antibodies against such CD179b damage cancer cells expressing CD179b, thereby completing the present invention.

[0010] The invention provides antibodies, antibodies for use, pharmaceutical compositions comprising antibodies and DNA encoding antibodies, all as defined in the claims.

[0011] The present invention provides an antibody, for use in a method of therapy and/or prophylaxis of cancer, the antibody having immunoreactivity to a CD179b protein having the amino acid sequence shown in SEQ ID NO:3 wherein the antibody is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells and complement-dependent cytotoxicity (CDC) against CD179-expressing cells.

[0012] In its mode, the above cancer is a cancer expressing the CD 179b gene.

[0013] In another mode, the above cancer is leukemia or lymphoma.

[0014] In another mode, the antibody is a monoclonal antibody or a polyclonal antibody.

[0015] In another mode, the antibody is a human antibody, humanized antibody, chimeric antibody, single-chain antibody or bispecific antibody.

[0016] In another mode, the above antibody is an antibody comprising a heavy chain variable region having the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 and a light chain variable region having the amino acid sequences shown in SEQ ID NOs:106, 107 and 108, the antibody having immunoreactivity to a CD 179b protein.

[0017] In another mode, the above antibody is an antibody comprising a heavy chain variable region having the amino acid sequence shown in SEQ ID NO:105 and a light chain variable region having the amino acid sequence shown in SEQ ID NO:109, the antibody having immunoreactivity to a CD 179b protein.

[0018] The present invention further provides the following antibodies.

(i) An antibody comprising a heavy chain variable region having the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 and a light chain variable region having the amino acid sequences shown in SEQ ID NOs:106, 107 and 108, the antibody having immunoreactivity to a CD179b protein, wherein the antibody is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells and complement-dependent cytotoxicity (CDC) against CD179-expressing cells.

(ii) The antibody of (i) comprising a heavy chain variable region having the amino acid sequence shown in SEQ ID NO:105 and a light chain variable region having the amino acid sequence shown in SEQ ID NO:109

(iv) The antibodies of the above (i) and (ii), each of which is a humanized antibody, chimeric antibody, single-chain antibody or bispecific antibody.

The present invention further provides the following DNAs.

(v) A DNA encoding a polypeptide having the amino acid sequence shown in SEQ ID NO:105, or a DNA encoding the polypeptide.

(vi) A DNA encoding a polypeptide having the amino acid sequence shown in SEQ ID NO:109, or a DNA encoding

the polypeptide.

(vii) A DNA having the base sequence shown in SEQ ID NO:110.

(viii) A DNA having the base sequence shown in SEQ ID NO: 111.

Also disclosed are: (ix) A heavy-chain complementarity-determining region (CDR) polypeptide selected from the group consisting of the amino acid sequences shown in SEQ ID NOs:103, 104 and 102, or a DNA encoding the polypeptide.

(x) A light-chain complementarity-determining region (CDR) polypeptide selected from the group consisting of the amino acid sequences shown in SEQ ID NOs:106, 107 and 108, or a DNA encoding the polypeptide.

EFFECT OF THE INVENTION

[0019] The antibody against CD179b, which is used in the present invention damages cancer cells. Therefore, the antibody against CD 179b is useful for therapy and/or prophylaxis of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020]

Fig. 1 is a diagram showing the expression patterns of the gene encoding the CD179b protein in normal tissues and tumor cell lines. Reference numeral 1 represents the expression pattern of the gene encoding the CD179b protein; and reference numeral 2 represents the expression pattern of the GAPDH gene.

Fig. 2 is a diagram showing an anti-tumor effect of an antibody against CD 179b (anti-CD 179b monoclonal antibody #8) in nude mice to which a human cancer cell line Namalwa expressing CD179b was transplanted. Reference numeral 3 represents the size of the tumor in miceto which the anti-CD 179b monoclonal antibody #8 was administered; and reference numeral 4 represents the size of the tumor in mice to which PBS(-) was administered.

BEST MODE FOR CARRYING OUT THE INVENTION

[0021] The amino acid sequence shown in SEQ ID NO:3 in SEQUENCE LISTING disclosed in the present invention is the amino acid sequence of CD 179b isolated, by the SEREX method using serum from a patient dog from which a canine mammary gland cancer tissue-derived cDNA library was prepared, as a human homologous factor (homologue) of a polypeptide which binds to antibodies specifically existing in the serum derived from the cancer-bearing dog (see Example 1). The antibody against CD 179b used in the present invention may be any type of antibody as long as the antibody can exert an anti-tumor activity and is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells and complement-dependent cytotoxicity (CDC) against CD179-expressing cells, and examples thereof include monoclonal antibodies, polyclonal antibodies, synthetic antibodies, multispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies and single chain antibodies. These antibodies can be prepared by methods known to those skilled in the art. In the present invention, the antibody can preferably specifically bind to a CD179b protein, and, in cases where the subject is a human, the antibody is preferably a human antibody or a humanized antibody in order to avoid or suppress rejection reaction.

[0022] Here, the term "specifically bind to a CD179b protein" means that the antibody specifically binds to a CD179b protein and does not substantially bind to other proteins.

[0023] In the present invention, the antibody against CD 179b employed may be commercially available. Examples of known antibodies against human CD179b include clones such as GA170, H-60, HP6054, A-19, C-16, SLC1, SLC2, SLC3, SLC4 and HSL11, which are available.

[0024] The anti-tumor activity of the antibody which may be used in the present invention can be assayed in vitro by investigating whether or not the antibody shows cytotoxicity against tumor cells expressing the polypeptide via immunocytes or complement, as mentioned later.

[0025] Further, the subject of the present invention to be subjected to the therapy and/or prophylaxis of cancer is a mammal such as a human, pet animal, domestic animal or sport animal, and the subject is preferably human.

[0026] The terms "cancer" and "tumor" used in the present specification mean a malignant neoplasm, and are used interchangeably.

[0027] Preparation of antigens, preparation of antibodies, and pharmaceutical compositions, related to the present invention will now be described.

<Preparation of antigens for preparation of antibodies>

[0028] The animal species from which the protein or a fragment thereof used as a sensitizing antigen to obtain an

antibody against CD179b used in the present invention is derived is not restricted, and examples thereof include human, dog, bovine, mouse and rat. However, the animal species is preferably selected in consideration of the compatibility with the parent cells used for cell fusion, and, in general, a protein derived from a mammal, especially human, is preferred. For example, in cases where the CD179b is human CD179b, a human CD179b protein or a partial peptide thereof, cells

expressing human CD179b, or the like may be used.
[0029] The base sequences and the amino acid sequences of human CD179b and homologues thereof can be obtained by, for example, accessing GenBank (NCBI, USA) and using an algorithm such as BLAST or FASTA (Karlin and Altschul, Proc. Natl. Acad. Sci. U.S.A., 87:2264-2268, 1993; Altschul et al., Nucleic Acids Res., 25:3389-3402, 1997). CD179b is also called as $\lambda 5$, IGLL1, Vpreb2, LOC608248 or the like, but "CD 179b" is used as a representative in the present specification. For example, human CD179b is registered under the numbers such as NM_152855 and NM_020070; murine Vpreb2 is registered under the numbers such as NM_016983; and canine LOC608248 is registered under the numbers such as XM_845215.

[0030] In the present invention, in cases where the base sequence or the amino acid sequence of human CD179b is used as a standard, a nucleic acid or a protein is targeted which has a sequence showing a sequence identity of 50% to 100%, preferably 60% to 100%, more preferably 80% to 100%, still more preferably 90% to 100%, most preferably 95% to 100%, for example, 97% to 100%, 98% to 100%, 99% to 100% or 99.5% to 100% to the sequence shown in SEQ ID NO:1 or 3. Here, the term "% sequence identity" means the percentage (%) of identical amino acids (or bases) with respect to the total number of amino acids (or bases) when two sequences are aligned with each other such that the maximum similarity is achieved therebetween with or without introduction of a gap(s).

[0031] The length of the fragment of the CD 179b protein is not less than the length of amino acids of the epitope (antigenic determinant), which is the shortest unit recognized by the antibody, and less than the total length of the protein. The length of the epitope is normally within the range of 7 to 12 continuous amino acids.

[0032] The above-described human CD179b protein and polypeptides containing its partial peptides can be synthesized by a chemical synthesis method such as the Fmoc method (fluorenyl-methyloxycarbonyl method) or the tBoc method (t-butyloxycarbonyl method). Further, they can be synthesized by conventional methods using various types of commercially available peptide synthesizers. Further, the polypeptide of interest can be obtained using known genetic engineering techniques, by preparing a polynucleotide encoding the above polypeptide and incorporating the polynucleotide into an expression vector, which is then introduced into a host cell, followed by allowing the polypeptide to be produced in the host cell.

[0033] The polynucleotide encoding the above polypeptide can be easily prepared by a known genetic engineering technique or a conventional method using a commercially available nucleic acid synthesizer. For example, DNA having the base sequence shown in SEQ ID NO: 1 can be prepared by carrying out PCR using human chromosomal DNA or a human cDNA library as a template, and a pair of primers designed such that the base sequence shown in SEQ ID NO:1 can be amplified therewith. The reaction conditions for the PCR can be set appropriately, and examples thereof include, but are not limited to, repeating the reaction process of 94°C for 30 seconds (denaturation), 55°C for 30 seconds to 1 minute (annealing) and 72°C for 2 minutes (extension) for, for example, 30 cycles, followed by the reaction at 72°C for 7 minutes. Further, the desired DNA can be isolated by preparing an appropriate probe(s) or primer(s) based on the information of the base sequence and the amino acid sequence shown in SEQ ID NOs:1 and 3, respectively, in SEQUENCE LISTING in the present specification, and using the probe(s) or primer(s) for screening of a cDNA library of human or the like.

[0034] The cDNA library is preferably prepared from cells, an organ or a tissue expressing the protein of SEQ ID NO:3. Examples of such cells and a tissue include bone marrow, leukemia cells, breast cancer cells and lymphoma cells. The above-described operations such as preparation of the probe(s) or primer(s), construction of a cDNA library, screening of the cDNA library and cloning of the gene of interest are known to those skilled in the art, and can be carried out according to the methods described in, for example, Sambrook et al., Molecular Cloning, Second Edition, Current Protocols in Molecular Biology (1989). From the thus obtained DNA, a DNA encoding a human CD 179b protein or a partial peptide thereof can be obtained.

[0035] The above-described host cells may be any cells as long as they can express the above polypeptide, and examples of prokaryotic cells include, but are not limited to, *E. coli*, and examples of eukaryotic cells include, but are not limited to, mammalian cultured cells such as the monkey kidney cells COS 1, Chinese hamster ovary cells CHO, human fetal kidney cell line HEK 293 and mouse embryonic skin cell line NIH3T3; yeast cells such as budding yeasts and fission yeasts; silkworm cells; and *Xenopus* egg cells.

[0036] In cases where prokaryotic cells are used as the host cells, the expression vector employed in the prokaryotic cells has a replication origin, promoter, ribosome binding site, multicloning site, terminator, drug resistant gene, nutrient complementary gene and/or the like. Examples of the expression vector for *E. coli* include the pUC system, pBluescriptII, pET expression system and pGEX expression system. By incorporating a DNA encoding the above polypeptide into such an expression vector and transforming prokaryotic host cells with the vector, followed by culturing the resulting transformants, the polypeptide encoded by the DNA can be expressed in the prokaryotic host cells. In this process, the

polypeptide can also be expressed as a fusion protein with another protein (e.g., green fluorescent protein (GFP) or glutathione S-transferase (GST)).

[0037] In cases where eukaryotic cells are used as the host cells, an expression vector for eukaryotic cells having a promoter, splicing site, poly(A) addition site and/or the like is used as the expression vector. Examples of such an expression vector include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pcDNA3, pMSG and pYES2. In the same manner as described above, by incorporating a DNA encoding the above polypeptide into such an expression vector and transforming eukaryotic host cells with the vector, followed by culturing the resulting transformants, the polypeptide encoded by the DNA can be expressed in the eukaryotic host cells. In cases where pIND/V5-His, pFLAG-CMV-2, pEGFP-N 1, pEGFP-C1 or the like is used as the expression vector, the above polypeptide can be expressed as a fusion protein to which a tag such as His tag (e.g., (His)₆ to (His)₁₀), FLAG tag, myc tag, HA tag or GFP was added.

[0038] For the introduction of the expression vector into the host cells, well-known methods such as electroporation, the calcium phosphate method, the liposome method, the DEAE dextran method and microinjection can be used.

[0039] Isolation and purification of the polypeptide of interest from the host cells can be carried out by a combination of known separation operations. Examples of the known separation operations include, but are not limited to, treatment with a denaturant such as urea, or a surfactant; ultrasonication treatment; enzyme digestion; salting-out or solvent fractional precipitation; dialysis; centrifugation; ultrafiltration; gel filtration; SDS-PAGE; isoelectric focusing; ion-exchange chromatography; hydrophobic chromatography; affinity chromatography; and reversed-phase chromatography.

<The Structure of an Antibody>

[0040] An antibody is usually a heteropolymeric glycoprotein having at least two heavy chains and two light chains. Except for IgM, it is a heterotetrameric glycoprotein of about 150 kDa constituted by two identical light (L) chains and two identical heavy (H) chains. Typically, each light chain is linked to a heavy chain via a single disulfide covalent bond, but the number of disulfide bonds between the heavy chains varies among various immunoglobulin isotypes. Each of the heavy chains and the light chains also has intrachain disulfide bonds. Each heavy chain has a variable domain (VH region) in its one end, and the variable domain is followed by several constant regions. Each light chain has a variable domain (VL region), and has one constant region at the opposite end thereof. The constant region of each light chain is aligned with the first constant region of a heavy chain, and each light chain variable domain is aligned with a heavy chain variable domain. Each variable domain of an antibody has particular regions showing particular variabilities, called the complementarity-determining regions (CDRs), which give a binding specificity to the antibody. Parts in each variable region, which parts are relatively conserved are called the framework regions (FRs). Each of the complete variable domains of the heavy chains and the light chains has four FRs linked via three CDRs. In each heavy chain, the three CDRs are called CDR1, CDRH2 and CDRH3 in the order from the N-terminus, and, in each light chain, they are called CDRL1, CDRL2 and CDRL3 in a similar manner. For the binding specificity of an antibody against an antigen, CDRH3 is most important. Further, the CDRs in each strand are held together by the FR regions such that the CDRs are close to one another, thereby contributing to formation of an antigen-binding site together with the CDRs from another strand. Although the constant region does not directly contribute to binding of the antibody to an antigen, it shows various effector functions such as involvement in antibody-dependent cell-mediated cytotoxicity (ADCC), phagocytosis via binding to the Fcγ receptor, the half life/clearance rate via the Neonatal Fc receptor (FcRn), and complement-dependent cytotoxicity (CDC) via the C1q component of the complement cascade.

<Preparation of the Antibody>

[0041] The anti-CD 179b antibody in the present invention means an antibody having an immunological reactivity with the total length of the CD179b protein or a fragment thereof. Here, the term "immunological reactivity" means a property by which the antibody and a CD 179b antigen are bound to each other, and the function to damage (to cause death, suppression or regression of) tumors is exerted by such binding. That is, the type of the antibody used in the present invention is not restricted as long as the antibody can be bound to a CD179b protein to damage tumors such as leukemia, lymphoma and breast cancer.

[0042] Examples of the antibody include monoclonal antibodies, polyclonal antibodies, synthetic antibodies, multispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies and single chain antibodies

[0043] The antibody may be further modified by glycosylation, acetylation, formylation, amidation, phosphorylation, pegylation (PEG) and/or the like.

[0044] Preparation examples of various antibodies are described below.

[0045] In cases where the antibody is a monoclonal antibody, for example, a leukemia cell line Namalwa expressing CD 179b is administered to a mouse to immunize the mouse, and spleen is extracted from the mouse. Cells are separated and fused with mouse myeloma cells, and, from the obtained fused cells (hybridomas), a clone producing an antibody

having a cancer cell growth suppressing action is selected. By isolating the monoclonal antibody-producing hybridoma having a cancer cell growth suppressing action, and culturing the hybridoma, followed by purifying the antibody from the culture supernatant by a commonly-used affinity purification method, the antibody can be prepared.

[0046] A hybridoma which produces a monoclonal antibody can also be prepared, for example, as follows.

[0047] First, according to a known method, an animal is immunized with a sensitizing antigen. In general, the method is carried out by intraperitoneal or subcutaneous injection of the sensitizing antigen to a mammal. More particularly, the sensitizing antigen is diluted to an appropriate volume with PBS (Phosphate-Buffered Saline) or physiological saline and suspended, followed by mixing, as desired, an appropriate amount of a normal adjuvant such as Freund's complete adjuvant with the suspension. This is followed by emulsification, and then administration of the emulsion to a mammal every 4 to 21 days for several times. Further, it is also possible to use an appropriate carrier when the immunization with the sensitizing antigen is carried out.

[0048] After such immunization of a mammal and confirmation of increase in the serum level of the desired antibody, immunocytes are collected from the mammal and subjected to cell fusion. Examples of preferred immunocytes especially include spleen cells.

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

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

[0051] More particularly, the cell fusion is carried out, for example, in the presence of a cell fusion-promoting agent, in a normal nutrient medium. Examples of the fusion-promoting agent include polyethylene glycol (PEG) and Sendai virus (HVJ), and, in order to enhance the fusion efficiency, an auxiliary agent such as dimethylsulfoxide may also be added as desired.

[0052] The ratio between the immunocytes and the myeloma cells to be used may be arbitrarily set. For example, it is preferred to use 1 to 10 times more immunocytes than the myeloma cells. Examples of the medium which can be used for the cell fusion include the RPMI1640 medium which is preferred for the growth of the myeloma cell line; MEM medium; and other media normally used for this kind of cell culture. Further, a serum replacement such as fetal calf serum (FCS) can also be used in combination.

[0053] During the cell fusion, prescribed amounts of the immunocytes and the myeloma cells are mixed together well in the medium, and a PEG solution (with an average molecular weight of about 1000 to 6000, for example) preheated to about 37°C is added to a concentration of normally 30 to 60% (w/v), followed by mixing the resulting mixture to form the hybridoma of interest. Subsequently, by repeating the operation of successive addition of an appropriate medium and removal of the supernatant by centrifugation, cell fusion agents and the like which are not preferred for the growth of the hybridoma are removed.

[0054] The thus obtained hybridoma is selected by being cultured in a normal selection medium such as the HAT medium (a medium containing hypoxanthine, aminopterin and thymidine). The culture in the above HAT medium is continued for a length of time sufficient for the cells other than the hybridoma of interest (unfused cells) to die (normally, for several days to several weeks). Thereafter, a normal limiting dilution method is carried out for screening and cloning of a single hybridoma producing the antibody of interest.

[0055] In addition to the method in which the above hybridoma is obtained by immunizing a non-human animal with the antibody, there is also a method in which human lymphocytes, such as human lymphocytes infected with EB virus, are sensitized in vitro with a protein, protein-expressing cells or a lysate thereof, and the sensitized lymphocytes are fused with human-derived myeloma cells having a permanent division potential, for example, U266 (registration number TIB 196), to obtain a hybridoma producing a human antibody having a desired activity (cell growth suppression activity, for example).

[0056] The thus prepared hybridoma producing a monoclonal antibody can be subcultured in a normal medium, and can be stored in liquid nitrogen for a long period.

[0057] That is, the hybridoma can be prepared by a process wherein the desired antigen or cells expressing the desired antigen is/are used as a sensitizing antigen to carry out immunization according a conventional immunization method, thereby obtaining immunocytes, which are then fused with known parent cells by a conventional cell fusion method, followed by screening of monoclonal antibody-producing cells (hybridomas) by a conventional screening method.

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

[0059] A naturally occurring CD179b protein, or a recombinant CD179b protein expressed as a fusion protein with GST in a microorganism such as *E. coli*, or a partial peptide thereof is used for immunization of a small animal such as a mouse, human antibody-producing mouse or rabbit, and serum is obtained from the small animal. A polyclonal antibody is prepared by purifying the serum by, for example, ammonium sulfate precipitation, protein A and protein G columns,

[0060] Here, known examples of the human antibody-producing mouse include the KM mouse (Kirin Pharma/Medarex) and XenoMouse (Amgen). When such a mouse is immunized with a CD 179b protein or a fragment thereof, a complete human polyclonal antibody can be obtained from blood. Further, by removing spleen cells from the immunized mouse and subjecting the cells to the fusion method with myeloma cells, a human-type monoclonal antibody can be prepared.

[0061] The antigen can be prepared according to a method using animal cells (Japanese Translated PCT Patent Application Laid-open No. 2007-530068), a method using a baculovirus (e.g., WO98/46777), or the like. In cases where the immunogenicity of the antigen is low, the immunization may be carried out after binding the antigen to a macromolecule having immunogenicity, such as albumin.

[0062] Further, a gene recombinant antibody can also be used, which antibody was prepared by cloning the antibody gene from the hybridoma and incorporating it into an appropriate vector, which was then transfected to a host, followed by allowing the host to produce the antibody by the genetic recombination technique (for example, see Carl, A.K. Borrebaeck, James, W. Larrick, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990).

[0063] More particularly, cDNA of the variable region (V region) of the antibody is synthesized from mRNA of the hybridoma using a reverse transcriptase. After obtaining the DNA encoding the V region of the antibody of interest, the DNA is linked to DNA encoding the antibody constant region (C region) of interest, and the resultant is incorporated into an expression vector. Alternatively, the DNA encoding the V region of the antibody may be incorporated into an expression vector having the DNA of the antibody C region. The incorporation is carried out such that the expression is allowed under the controls by expression control regions such as an enhancer and/or a promoter. Subsequently, host cells can be transformed with this expression vector to allow expression of the antibody.

[0064] The anti-CD 179b antibody of the present invention is preferably a monoclonal antibody. However, it may also be a polyclonal antibody, genetically modified antibody (such as a chimeric antibody or humanized antibody) or the like.

[0065] Examples of the monoclonal antibody include human monoclonal antibodies and non-human animal monoclonal antibodies (e.g., mouse monoclonal antibodies, rat monoclonal antibodies and chicken monoclonal antibodies). The monoclonal antibody can be prepared by culturing a hybridoma obtained by fusion of spleen cells from a non-human mammal (e.g., mouse or human antibody-producing mouse) immunized with a CD179b protein, with myeloma cells. In Examples below, a mouse monoclonal antibody #8 was prepared, with which an anti-tumor effect was confirmed. The antibody #8 has a heavy chain variable (VH) region having the amino acid sequence shown in SEQ ID NO:105 and a light chain variable region (VL) having the amino acid sequence shown in SEQ ID NO:109. Here, the VH region has the amino acid sequences shown in SEQ ID NO:103 (CDR1), SEQ ID NO:104 (CDR2) and SEQ ID NO:102 (CDR3); and the VL region has the amino acid sequences shown in SEQ ID NO:106 (CDR1), SEQ ID NO:107 (CDR2) and SEQ ID NO:108 (CDR3).

[0066] A chimeric antibody is an antibody prepared by combining sequences derived from different animals. Examples thereof include an antibody having variable regions of the heavy chain and the light chain of a mouse antibody and the constant regions of the heavy chain and the light chain of a human antibody. Preparation of the chimeric antibody can be carried out using a known method. For example, it can be obtained by linking a DNA encoding an antibody V region to a DNA encoding a human antibody C region, followed by incorporating the resultant to an expression vector and transfecting the vector to a host, thereby allowing production of a chimeric antibody.

[0067] Examples of the polyclonal antibody include antibodies obtained by immunizing a human antibody-producing animal (mouse, for example) with a CD 179b protein

[0068] A humanized antibody is a modified antibody also called as a reshaped human antibody. A humanized antibody can be constructed by transplantation of the CDRs of an antibody derived from an immunized animal to the complementarity-determining regions of a human antibody. A common genetic recombination technique therefor is known.

[0069] More particularly, a DNA sequence designed such that the CDRs of a mouse antibody are linked to the framework regions (FRs) of a human antibody is synthesized by the PCR method from several oligonucleotides prepared such that the oligonucleotides have overlapped regions in their ends. The obtained DNA is linked to a DNA encoding the human antibody constant region, and the resultant is incorporated into an expression vector, followed by introducing the vector to a host, to obtain a humanized antibody (see European Patent Application Publication No. EP 239400 and International Patent Application Publication No. WO96/02576). The FRs of the human antibody linked via the CDRs are selected such that the complementarity-determining regions form a good antigen-binding site. As required, amino acids in the framework regions in the variable regions of the antibody may be substituted such that the complementarity-determining regions of the reshaped human antibody form an appropriate antigen-binding site (Sato, K. et al., Cancer Res. (1993) 53, 851-856). Further, the framework regions may be substituted with framework regions derived from various human

antibodies (see International Patent Application Publication No. WO99/51743).

[0070] After preparation of a chimeric antibody or a humanized antibody, amino acids in the variable regions (FRs, for example) and/or the constant regions may be substituted with other amino acids.

[0071] The number of the amino acids to be substituted is, for example, less than 15, less than 10, not more than 8, not more than 7, not more than 6, not more than 5, not more than 4, not more than 3 or not more than 2, preferably 1 to 5, more preferably 1 or 2, and the substituted antibody should be functionally equivalent to the unsubstituted antibody. The substitutions are preferably conservative amino acid substitutions, which are substitutions among amino acids having similar properties of charges, side chains, polarities, aromaticities and/or the like. The amino acids having similar properties can be classified, for example, into basic amino acids (arginine, lysine and histidine), acidic amino acids (aspartic acid and glutamic acid), uncharged polar amino acids (glycine, asparagine, glutamine, serine, threonine, cysteine and tyrosine), nonpolar amino acids (leucine, isoleucine, alanine, valine, proline, phenylalanine, tryptophan and methionine), branched chain amino acids (threonine, valine and isoleucine) and aromatic amino acids (phenylalanine, tyrosine, tryptophan and histidine).

[0072] Examples of the modified antibody include antibodies bound to various molecules such as polyethylene glycol (PEG). In the modified antibody of the present invention, the substance to which the antibody is bound is not restricted. Such a modified antibody can be obtained by chemical modification of the obtained antibody. These methods are already established in the art.

[0073] Here, the term "functionally equivalent" means, for example, that the subject antibody has a similar biological or biochemical activity, more particularly, a function to damage tumors, and does not essentially cause the rejection reaction when it is applied to human. Examples of such an activity may include a cell growth suppressing activity and a binding activity.

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

[0075] The antibody which recognizes the epitope of the CD179b protein to be recognized by the above-described anti-CD 179b antibody can be obtained by a method known to those skilled in the art. Examples of the method by which it can be obtained include a method wherein the epitope of the CD 179b protein recognized by the anti-CD179b antibody is determined by a normal method (e.g., epitope mapping) and an antibody is prepared using as an immunogen a polypeptide having an amino acid sequence included in the epitope; and a method wherein the epitope of the antibody is determined by a normal method, followed by selecting an antibody having the same epitope as that of the anti-CD179b antibody. Here, the term "epitope" means a polypeptide fragment having antigenicity or immunogenicity in a mammal, preferably human, and its minimum unit has about 7 to 12 amino acids.

[0076] The affinity constant K_a (K_{on}/K_{off}) of the antibody of the present invention is preferably at least 10^7 M⁻¹, at least 10^8 M⁻¹, at least 5×10^8 M⁻¹, at least 10^9 M⁻¹, at least 5×10^9 M⁻¹, at least 10^{10} M⁻¹, at least 5×10^{10} M⁻¹, at least 10^{11} M⁻¹, at least 5×10^{11} M⁻¹, at least 10^{12} M⁻¹, at least 10^{13} M⁻¹.

[0077] The antibody of the present invention can be conjugated with an antitumor agent. The binding between the antibody and the antitumor agent can be carried out via a spacer having a group (e.g., succinimidyl group, formyl group, 2-pyridyldithio group, maleimidyl group, alkoxycarbonyl group or hydroxy group) reactive with an amino group, carboxyl group, hydroxy group, thiol group and/or the like.

[0078] Examples of the antitumor agent include the following antitumor agents known in literatures and the like, that is, paclitaxel, doxorubicin, daunorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolmelamine, bullatacin, bullatacinone, camptothecin, bryostatin, calystatin, cryptophycin 1, cryptophycin 8, dolastatin, duocarmycin, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxyhydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, dynemicin, clodronate, esperamicin, aclacinomycin, actinomycin, authramycin, azaserine, bleomycin, cactinomycin, carabycin, carminomycin, carzinophillin, chromomycin, dactinomycin, detorbicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN, epirubicin, esorubicin, idarubicin, marcelomycin, mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine and floxuridine; androgens such as calusterone, dromostanolone propionate, epitioestanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone, aldophospha-

mide glycoside, aminolevulinic acid, eniluracil, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, lentinan, lonidamine, maytansine, ansamitocine, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, schizophyllan, spirogermanium, tenuazonic acid, triaziquone, roridine A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, doxetaxel, chlorambucil, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, oxaliplatin, carboplatin, vinblastine, etoposide, ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, irinotecan, topoisomerase inhibitors, difluoromethylornithine (DMFO), retinoic acid and capecitabine, and pharmaceutically acceptable salts and derivatives thereof.

[0079] Alternatively, the antibody of the present invention can be linked to a known radioisotope described in a literature or the like, such as At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³² or Lu. The radioisotope is preferably effective for therapy and/or diagnosis of a tumor.

[0080] The antibody of the present invention is an antibody having an immunological reactivity with CD179b, or an antibody which specifically recognizes CD179b. The antibody should be an antibody having a structure by which the rejection reaction can be mostly or completely avoided in the subject animal to which the antibody was administered. Examples of such an antibody include, for example, in cases where the subject animal is human, human antibodies, humanized antibodies, chimeric antibodies (e.g., human-mouse chimeric antibodies), single chain antibodies and bispecific antibodies. Each of these antibodies is a recombinant antibody wherein: each variable region in the heavy chain and the light chain is derived from a human antibody; each variable region in the heavy chain and the light chain is constituted by the complementarity-determining regions (CDR1, CDR2 and CDR3) of an antibody derived from a non-human animal and the framework regions derived from a human antibody; or each variable region in the heavy chain and the light chain is derived from a non-human animal; which recombinant antibody has human antibody-derived constant regions in the heavy chain and the light chain. The first two antibodies are preferred.

[0081] These recombinant antibodies can be prepared as follows. A DNA encoding a monoclonal antibody (for example, human monoclonal antibody, mouse monoclonal antibody, rat monoclonal antibody or chicken monoclonal antibody) against human CD179b is cloned from antibody-producing cells such as hybridomas, and, using this as a template, DNAs encoding the light chain variable region and the heavy chain variable region of the antibody is prepared by, for example, the RT-PCR method, followed by determining the sequence of the variable region or the sequences of CDR1, CDR2 and CDR3 in each of the light chain and the heavy chain according to the Kabat EU numbering system (Kabat et al., Sequences of Proteins of Immunological Interest, 5Th Ed. Public Health Service, National Institute of Health, Bethesda, Md. (1991)). Further, DNAs encoding the respective variable regions or DNAs encoding the respective CDRs are prepared using the genetic recombination technique (Sambrook et al., Molecular Cloning, Second Edition, Current Protocols in Molecular Biology (1989)) or a DNA synthesizer. Here, the above-described human monoclonal antibody-producing hybridoma can be prepared by immunizing a human antibody-producing animal (e.g., mouse) with human CD179b, followed by fusing spleen cells excised from the immunized animal with myeloma cells. In addition, as required, DNAs encoding the variable region and the constant region in the light chain or the heavy chain derived from a human antibody are prepared using the genetic recombination technique or a DNA synthesizer.

[0082] In the case of a humanized antibody, a DNA encoding the humanized antibody can be prepared by a process wherein the CDR sequences in a DNA encoding the variable region of the light chain or the heavy chain derived from a human antibody are substituted with the corresponding CDR sequences of an antibody derived from a non-human animal (e.g., mouse, rat or chicken) to prepare a DNA, and the thus obtained DNA is linked to a DNA encoding the constant region in the light chain or the heavy chain, respectively, derived from a human antibody.

[0083] In the case of a chimeric antibody, a DNA encoding the chimeric antibody can be prepared by a process wherein a DNA encoding the variable region in the light chain or the heavy chain derived from a non-human animal (e.g., mouse, rat or chicken) is linked to a DNA encoding the constant region of the light chain or the heavy chain, respectively, derived from a human antibody.

[0084] In the case of a single-chain antibody, which is an antibody having a heavy chain variable region and a light chain variable region linearly linked to each other via a linker, a DNA encoding the single-chain antibody can be prepared by a process wherein a DNA encoding the heavy chain variable region, a DNA encoding the linker and a DNA encoding the light chain variable region are linked together. Here, each of the heavy chain variable region and the light chain variable region is either derived from a human antibody or derived from a human antibody in which only the CDRs were replaced by the CDRs of an antibody derived from a non-human animal (e.g., mouse, rat or chicken). Further, the linker has 12 to 19 amino acids, and examples thereof include (G₄S)₃ having 15 amino acids (Kim, GB. et al., Protein Engineering Design and Selection 2007, 20(9):425-432).

[0085] In the case of a bispecific antibody (diabody), which is an antibody capable of binding specifically to two different epitopes, a DNA encoding the bispecific antibody can be prepared, for example, by a process wherein a DNA encoding a heavy chain variable region A, a DNA encoding a light chain variable region B, a DNA encoding a heavy chain variable region B and a DNA encoding a light chain variable region A are linked together in this order (however, the DNA encoding

a light chain variable region B and the DNA encoding a heavy chain variable region B are linked to each other via a DNA encoding a linker as described above). Here, each of the heavy chain variable region and the light chain variable region is either derived from a human antibody or derived from a human antibody in which only the CDRs were replaced by the CDRs of an antibody derived from a non-human animal (e.g., mouse, rat or chicken).

[0086] A recombinant antibody can be prepared by incorporating the thus prepared recombinant DNA(s) into one or more appropriate vector(s) and introducing the resulting vector(s) into host cells (e.g., mammalian cells, yeast cells and insect cells), followed by allowing (co-)expression of the recombinant DNA(s) (P.J. Delves., ANTIBODY PRODUCTION ESSENTIAL TECHNIQUES., 1997 WILEY; P. Shepherd and C. Dean., Monoclonal Antibodies., 2000 OXFORD UNIVERSITY PRESS; J.W. Goding., Monoclonal Antibodies: principles and practice., 1993 ACADEMIC PRESS).

[0087] The antibody of the present invention prepared by the above method is an antibody comprising, for example, a heavy chain variable region having the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 and a light chain variable region having the amino acid sequences shown in SEQ ID NOs:106, 107 and 108. Here, the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 are those for CDR1, CDR2 and CDR3, respectively, of a mouse antibody heavy chain variable region, and the amino acid sequences shown in SEQ ID NOs:106, 107 and 108 are those for CDR1, CDR2 and CDR3, respectively, of a mouse antibody light chain variable region. Therefore, the humanized antibody, chimeric antibody, single-chain antibody or bispecific antibody of the present invention is the following antibody, for example.

(i) An antibody comprising: a heavy chain variable region having the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 and the amino acid sequences of the framework regions derived from a human antibody; and a light chain variable region having the amino acid sequences shown in SEQ ID NOs:106, 107 and 108 and the amino acid sequences of the framework regions derived from a human antibody.

(ii) An antibody comprising: a heavy chain variable region having the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 and the amino acid sequences of the framework regions derived from a human antibody; a heavy chain constant region having an amino acid sequence derived from a human antibody; a light chain variable region having the amino acid sequences shown in SEQ ID NOs:106, 107 and 108 and the amino acid sequences of the framework regions derived from a human antibody; and a light chain constant region having an amino acid sequence derived from a human antibody.

(iii) An antibody comprising: a heavy chain variable region having the amino acid sequence shown in SEQ ID NO:105; and a light chain variable region having the amino acid sequence shown in SEQ ID NO:109.

(iv) An antibody comprising: a heavy chain variable region having the amino acid sequence shown in SEQ ID NO:105; a heavy chain constant region having an amino acid sequence derived from a human antibody; a light chain variable region having the amino acid sequence shown in SEQ ID NO:109; and a light chain constant region having an amino acid sequence derived from a human antibody.

[0088] Sequences of the constant regions and the variable regions of human antibody heavy chains and light chains can be obtained from, for example, NCBI (USA: GenBank, UniGene and the like). Examples of the sequences which may be referred to include the accession number J00228 for the human IgG1 heavy chain constant region, the accession number J00230 for the human IgG2 heavy chain constant region, the accession number X03604 for the human IgG3 heavy chain constant region, the accession number K01316 for the human IgG4 heavy chain constant region, the accession numbers V00557, X64135, X64133 and the like for the human light chain κ constant region, and the accession numbers X64132, X64134 and the like for the human light chain λ constant region.

[0089] The above antibody preferably has cytotoxic activity and therefore can exert an anti-tumor effect.

[0090] Further, the specific sequences of the variable regions of the heavy chain and the light chain and the CDRs in the above antibodies are presented for the illustration purpose only, and it is apparent that they are not restricted to the specific sequences. A hybridoma which can produce another human antibody or non-human animal antibody (e.g., mouse antibody) against human CD179b is prepared, and the monoclonal antibody produced by the hybridoma is recovered, followed by judging whether or not it is an antibody of interest using as indices its immunological affinity and cytotoxicity to human CD 179b. By this, a monoclonal antibody-producing hybridoma of interest is identified, and DNAs encoding the variable regions of the heavy chain and the light chain of the antibody of interest are prepared from the hybridoma as described above, followed by determining the sequences of the DNAs and then using the DNAs for preparation of the another antibody.

[0091] Further, the above antibody of the present invention may have substitution, deletion and/or addition of 1 or several (preferably, 1 or 2) amino acid(s) especially in a framework region sequence(s) and/or constant region sequence(s) in each of the antibodies (i) to (iv) above, as long as the antibody has a specificity allowing specific recognition of CD179b. Here, the term "several" means 2 to 5, preferably 2 or 3.

[0092] The present invention further provides a DNA encoding the above antibody of the present invention, a DNA encoding the heavy chain or the light chain of the above antibody or a DNA encoding the variable region of the heavy

chain or the light chain of the above antibody. Examples of such a DNA include: DNAs encoding heavy chain variable regions having the base sequences encoding the amino acid sequences shown in SEQ ID NOs:103, 104 and 102; DNAs encoding light chain variable regions having the base sequences encoding the amino acid sequences shown in SEQ ID NOs:106, 107 and 108; and the like.

[0093] Since the complementarity-determining regions (CDRs) encoded by DNAs having these sequences are regions which determine the specificity of the antibody, the sequences encoding the other regions in the antibody (that is, the constant regions and the framework regions) may be those derived from another antibody. Here, although the another antibody includes antibodies derived from non-human organisms, it is preferably derived from human in view of reduction of side effects. That is, in the above-described DNA, the regions encoding the respective framework regions and the constant regions of the heavy chain and the light chain preferably have base sequences encoding corresponding amino acid sequences derived from a human antibody.

[0094] Other examples of the DNA encoding the antibody of the present invention include DNAs encoding the heavy chain variable region having a base sequence encoding the amino acid sequence shown in SEQ ID NO:105 and DNAs wherein the region encoding the light chain variable region has a base sequence encoding the amino acid sequence shown in SEQ ID NO:109. Here, examples of the base sequence encoding the amino acid sequence shown in SEQ ID NO:105 include the base sequence shown in SEQ ID NO:110. Further, examples of the base sequence encoding the amino acid sequence shown in SEQ ID NO:109 include the base sequence shown in SEQ ID NO:111. Among these DNAs, preferred are those comprising the region encoding the constant region of each of the heavy chain and the light chain, having a base sequence encoding a corresponding amino acid sequence derived from a human antibody.

[0095] The DNA of the present invention can be obtained by, for example, the above method or the following method. First, from a hybridoma related to the antibody of the present invention, total RNA is prepared using a commercially available RNA extraction kit, and cDNA is synthesized by a reverse transcriptase using random primers or the like. Subsequently, by the PCR method using as primers oligonucleotides having sequences conserved in the variable region of each of a known mouse antibody heavy chain gene and light chain gene, cDNAs encoding the antibody are amplified. The sequence encoding each constant region can be obtained by amplifying a known sequence by the PCR method. The base sequences of the DNAs can be determined by a conventional method by, for example, incorporating the sequences into plasmids or phages for sequence determination.

[0096] The anti-tumor effect of the anti-CD 179b antibody used in the present invention against CD179b-expressing cancer cells is considered to be caused by the following mechanism.

[0097] The antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells against CD179b-expressing cells; and

the complement-dependent cytotoxicity (CDC) against CD 179b-expressing cells.

[0098] Thus, evaluation of the activity of the anti-CD 179b antibody used in the present invention can be carried out, as particularly shown in Examples below, by measuring the above-described ADCC activity or CDC activity against cancer cells expressing CD 179b in vitro.

[0099] Since the anti-CD179b antibody used in the present invention binds to a CD 179b protein on cancer cells and exhibits an anti-tumor action due to the above activities, the antibody is considered to be effective for therapy and/or prophylaxis of cancer. That is, the present invention provides a pharmaceutical composition for therapy and/or prophylaxis of cancer comprising as an effective component an anti-CD 179b antibody. In cases where the anti-CD 179b antibody is used for the purpose of administration to a human body (antibody therapy), the antibody is preferably prepared as a human antibody or a humanized antibody in order to reduce its immunogenicity.

[0100] A higher binding affinity of the anti-CD 179b antibody to the CD 179b protein on the cancer cell surface causes a stronger anti-tumor activity by the anti-CD 179b antibody. Thus, if an anti-CD 179b antibody having a higher binding affinity to the CD179b protein can be obtained, a higher anti-tumor effect can be expected, and therefore the antibody can be applied as a pharmaceutical composition for the purpose of therapy and/or prophylaxis of cancer. In terms of the higher binding affinity, the affinity constant K_a (K_{on}/K_{off}) is preferably at least 10^7 M⁻¹, at least 10^8 M⁻¹, at least 5×10^8 M⁻¹, at least 10^9 M⁻¹, at least 5×10^9 M⁻¹, at least 10^{10} M⁻¹, at least 5×10^{10} M⁻¹, at least 10^{11} M⁻¹, at least 5×10^{11} M⁻¹, at least 10^{12} M⁻¹, at least 10^{13} M⁻¹, as previously mentioned.

<Pharmaceutical Composition>

[0101] The target of the pharmaceutical composition of the present invention for therapy and/or prophylaxis of cancer is not restricted as long as it is a cancer (cell) expressing the CD179b gene, and preferably a cancer (cell) selected from the group consisting of leukemia, lymphoma and breast cancer, including also mammary gland cancer, combined mammary gland cancer, mammary gland malignant mixed tumor, intraductal papillary adenocarcinoma, mastocytoma, chronic lymphocytic leukemia, gastrointestinal lymphoma, digestive organ lymphoma and small/medium cell lymphoma.

[0102] Further, the antibody used in the present invention can be used for therapy and/or prophylaxis of the above-described cancers.

[0103] When the antibody used in the present invention is used as a pharmaceutical composition, it can be formulated by a method known to those skilled in the art. For example, it can be parenterally used in the form of an injection solution containing a sterile solution or suspension prepared with another pharmaceutically acceptable liquid. For example, the composition may be used in combination with a pharmaceutically acceptable carrier(s) and/or medium/media, such as sterile water, physiological saline, vegetable oil, emulsifier, suspending agent, surfactant, stabilizer, flavoring agent, excipient, vehicle, antiseptic and/or binder, which is/are mixed into the form of a unit dose required for carrying out formulation which is generally accepted. The amount of the effective component in the formulation is determined such that an appropriate volume is obtained within the prescribed range.

[0104] The sterile composition for injection can be prescribed using a vehicle such as distilled water for injection, according to a conventional formulation method.

[0105] Examples of the aqueous solution include isotonic solutions containing physiological saline, glucose and/or an adjunct(s) such as D-sorbitol, D-mannose, D-mannitol and/or sodium chloride, which may be used in combination with an appropriate solubilizer(s) such as an alcohol, in particular, ethanol; polyalcohol such as propylene glycol; polyethylene glycol; nonionic surfactant such as polysorbate 80 (TM); and/or HCO-60.

[0106] Examples of the oily liquid include sesame oils and soybean oils, which may be used in combination with benzyl benzoate or benzyl alcohol as a solubilizer. Further, a buffering agent such as phosphate buffer or sodium acetate buffer; soothing agent such as procaine hydrochloride; and/or stabilizer such as benzyl alcohol, phenol or antioxidant may also be blended. The prepared injection solution is usually filled into an appropriate ampoule.

[0107] The administration is carried out orally or parenterally, preferably parenterally, and particular examples thereof include the injection solution type, nasal administration type, pulmonary administration type and percutaneous administration type. Examples of the injection solution type include intravenous injection, intramuscular injection, intraperitoneal administration and subcutaneous injection, by which the injection solution can be administered systemically or topically.

[0108] Further, the method of administration can be appropriately selected depending on the age, symptom, sex and the like of the patient. The dose of the pharmaceutical composition containing the antibody can be selected within the range of, for example, 0.0001 mg to 1000 mg per 1 kg of the body weight per one time. Alternatively, the dose can be selected within the range of 0.001 to 100000 mg/body per patient, but the dose is not restricted to these values. The dose and the method of administration vary depending on the body weight, age, symptom and the like of the patient, and those skilled in the art can appropriately select them.

<Polypeptide and DNA>

[0109] The present invention further provides the following DNAs related to the above antibody.

- (i) A polypeptide having the amino acid sequence shown in SEQ ID NO:105, and a DNA encoding the polypeptide.
- (ii) A polypeptide having the amino acid sequence shown in SEQ ID NO:109, and a DNA encoding the polypeptide.
- (iii) A DNA having the base sequence shown in SEQ ID NO:110.
- (iv) A DNA having the base sequence shown in SEQ ID NO:111.

Also disclosed are:

- (v) A heavy chain CDR polypeptide selected from the group consisting of the amino acid sequences shown in SEQ ID NOs:103, 104 and 102, and a DNA encoding the polypeptide.
- (vi) A light chain CDR polypeptide selected from the group consisting of the amino acid sequences shown in SEQ ID NOs:106, 107 and 108, and a DNA encoding the polypeptide.

[0110] These polypeptides and DNAs may be prepared using the genetic recombination technique as described above.

EXAMPLES

[0111] The present invention will now be described concretely by way of Examples, but the scope of the present invention is not restricted by these particular examples.

Example 1: Identification of a Novel Cancer Antigen by the SEREX Method

(1) Preparation of a cDNA Library

[0112] From a canine mammary gland cancer tissue removed by surgery, total RNA was extracted by the Acid guanidium-Phenol-Chloroform method, and poly(A)⁺ RNA was purified using the Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) according to the protocol described in the attached instructions.

[0113] Using the thus obtained mRNA (5 µg), a canine mammary gland cancer-derived cDNA phage library was

synthesized. For preparation of the cDNA phage library, cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit and ZAP-cDNA GigapackIII Gold Cloning Kit (manufactured by STRATAGENE) were used according to the protocols described in the attached instructions. The size of the prepared cDNA phage library was 2.99×10^5 pfu/ml.

(2) Screening of the cDNA Library by Serum

[0114] Using the canine mammary gland cancer-derived cDNA phage library prepared as described above, immunoscreening was carried out. More particularly, host *E. coli* (XL1-Blue MRF') was infected with the library such that 2340 clones were included in a $\Phi 90 \times 15$ mm NZY agarose plate, followed by culture at 42°C for 3 to 4 hours to allow formation of plaques. The plate was covered with a nitrocellulose membrane (Hybond C Extra; manufactured by GE Healthcare Bio-Science) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours, to allow induction and expression of proteins, thereby transferring the proteins to the membrane. Thereafter, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl pH 7.5) supplemented with 0.5% non-fat dry milk, followed by being shaken at 4°C overnight to suppress nonspecific reactions. This filter was allowed to react with 500-fold diluted patient dog serum at room temperature for 2 to 3 hours.

[0115] As the above-described patient dog serum, a total of 3 serum samples were used which were collected from each of the dog from which the above mammary gland cancer was removed and another mammary gland cancer patient dog. These sera were stored at -80°C and pretreated immediately before use. The pretreatment of the sera was carried out by the following method. That is, host *E. coli* (XL1-Blue MRF') was infected with λ ZAP Express phage into which no exogenous gene was inserted, and cultured on a NZY plate at 37°C overnight. Subsequently, 0.2 M NaHCO₃ buffer (pH 8.3) containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C for 15 hours, followed by recovering the supernatant as an *E. coli*/phage extract. Thereafter, the recovered *E. coli*/phage extract was passed through a NHS-column (manufactured by GE Healthcare Bio-Science) to immobilize the proteins derived from the *E. coli*/phage. The serum from the patient dog was passed through this protein-immobilized column and allowed to react with the proteins, thereby removing antibodies that adsorb to *E. coli* and the phage from the serum. The serum fraction passed through the column without being adsorbed was 500-fold diluted with TBS supplemented with 0.5% non-fat dry milk, and the resulting dilution was used as a material for the immunoscreening.

[0116] The membrane to which the thus treated serum and the above-described fusion proteins were blotted was washed with TBS-T (0.05% Tween 20/TBS) 4 times, and a goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated; manufactured by BETHYL Laboratories, Inc.) which was 5000-fold diluted with TBS supplemented with 0.5% non-fat dry milk was allowed, as a secondary antibody, to react at room temperature for 1 hour. Detection was carried out by an enzymatic coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche), and colonies whose positions were identical to those of positive sites of the coloring reaction were collected from the $\Phi 90 \times 15$ mm NZY-agarose plate, and dissolved into 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO₄, 50 mM Tris-HCl, 0.01% gelatin, pH 7.5). The second and third screenings were carried out by repeating the same method as described above until the colonies positive in the coloring reaction became single colonies, thereby isolating 45 positive clones after screening of 92820 phage clones reactive with IgG in the serum.

Homology Search of the Isolated Antigen Genes

[0117] To subject the 45 positive clones isolated by the above method to sequence analysis, an operation to convert the phage vector to a plasmid vector was carried out. More particularly, 200 μ l of a solution prepared such that the host *E. coli* (XL1-Blue MRF') was contained to an absorbance OD₆₀₀ of 1.0, 250 μ l of the purified phage solution and 1 μ l of ExAssist helper phage (manufactured by STRATAGENE) were mixed together, and the resulting mixture was allowed to react at 37°C for 15 minutes, followed by adding 3 ml of LB broth thereto and culturing the resultant at 37°C for 2.5 to 3 hours. This was immediately followed by 20 minutes of incubation in a water bath at 70°C and centrifugation at 1000 $\times$ g for 15 minutes, after which the supernatant was collected as a phagemid solution. Subsequently, 200 μ l of a solution prepared such that the phagemid host *E. coli* (SOLR) was contained to an absorbance OD₆₀₀ of 1.0 and 10 μ l of the purified phagemid solution were mixed together, and the resulting mixture was allowed to react at 37°C for 15 minutes, followed by plating a 50 μ l aliquot of the resultant on LB agar medium supplemented with ampicillin (50 μ g/ml final concentration) and culturing at 37°C overnight. Single colonies of the transformed SOLR were picked up and cultured in LB medium supplemented with ampicillin (50 μ g/ml final concentration) at 37°C, followed by purifying plasmid DNAs having inserts of interest using QIAGEN plasmid Miniprep Kit (manufactured by QIAGEN).

[0118] Each purified plasmid was subjected to analysis of the full-length sequence of the insert by the primer walking method using the T3 primer shown in SEQ ID NO:94 and the T7 primer shown in SEQ ID NO:95. By this sequence analysis, the gene sequences shown in the even number IDs of SEQ ID NOs:4 to 92 were obtained. Using the base sequences and the amino acid sequences (odd number IDs of SEQ ID NOs: 5 to 93) of these genes, homology search against known genes were carried out using a homology search program BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>),

and, as a result, it was revealed that all the obtained 45 genes were those encoding CD 179b. The homologies among the 45 genes were 94 to 99% in terms of the base sequences and 96 to 99% in terms of the amino acid sequences. The homologies between these genes and the gene encoding a human homologous factor were 62 to 82% in terms of the base sequences and 69 to 80% in terms of the amino acid sequences, in the region translated to a protein. The base sequence of the human homologous factor is shown in SEQ ID NO:1, and the amino acid sequences of the human homologous factor are shown in SEQ ID NOs:2 and 3.

(4) Analysis of Gene Expression in Each Tissue

[0119] Expressions of the genes obtained by the above method in dog and human normal tissues and various cell lines were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, from 50 to 100 mg of each tissue or $5-10 \times 10^6$ cells of each cell line, total RNA was extracted using the TRIZOL reagent (manufactured by INVITROGEN) according to the protocol described in the attached instructions. Using this total RNA, cDNA was synthesized by the Superscript First-Strand Synthesis System for RT-PCR (manufactured by INVITROGEN) according to the protocol described in the attached instructions. As the cDNAs of human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by INVITROGEN), QUICK-Clone cDNA (manufactured by CLONETECH) and Large-Insert cDNA Library (manufactured by CLONETECH) were used. The PCR reaction was carried out as follows, using primers specific to the obtained dog genes (shown in SEQ ID NOs:96 and 97) and their human homologous gene (shown in SEQ ID NOs:98 and 99). That is, reagents and an attached buffer were mixed such that concentrations/amounts of 0.25 μ l of a sample prepared by the reverse transcription reaction, 2 μ M each of the above primers, 0.2 mM each of dNTPs, and 0.65 U ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) were attained in a total volume of 25 μ l, and the reaction was carried out by repeating 30 cycles of 94°C for 30 seconds, 60°C for 30 seconds and 72°C for 30 seconds using a Thermal Cycler (manufactured by Bio-Rad Laboratories, Inc.). The above-described primers specific to genes having the base sequences shown in SEQ ID NOs: 96 and 97 were for amplification of the positions 32 to 341 in the base sequence shown in SEQ ID NO:4, and for amplification of the region common to all the dog CD 179b genes shown in the even number IDs of SEQ ID NOs: 4 to 92. Further, the primers specific to genes having the base sequences shown in SEQ ID NOs:98 and 99 were for amplification of the positions 216 to 738 in the base sequence shown in SEQ ID NO:1. As a control for comparison, primers specific to GAPDH (shown in SEQ ID NOs:100 and 101) were used at the same time. As a result, as shown in Fig. 1, the obtained dog genes did not show expression in normal dog tissues at all, but showed strong expression in canine breast cancer tissues. In terms of expression of the human homologous gene, bone marrow was the only human normal tissue wherein its expression was confirmed, but, in human cancer cells, its expression was detected in leukemia cell lines and breast cancer cell lines, so that specific expression of CD179b in the leukemia cell lines and the breast cancer cell lines was confirmed.

[0120] In Fig. 1, reference numeral 1 in the ordinate represents the expression pattern of the gene identified as above, and reference numeral 2 represents the expression pattern of the GAPDH gene as the control for comparison.

(5) Analysis of Expression of the Antigen Protein on Cancer Cells

[0121] Subsequently, each cancer cell line wherein expression of the CD179b gene was confirmed was investigated for whether or not the CD 179b protein is expressed on the cell surface. In a 1.5 ml microcentrifuge tube, 10^6 cells of each human cancer cell line for which expression of the gene was observed were placed, which tube was then centrifuged. To this tube, 5 μ l of mouse anti-human CD 179b antibody (clone name: GA170; manufactured by Santa Cruz Biotechnology) was added, and the resultant was suspended in 95 μ l of PBS supplemented with 0.1% fetal calf serum, followed by leaving the resulting suspension to stand on ice for 1 hour. After washing the cells with PBS, the cells were suspended in 5 μ l of FITC-labeled rabbit anti-mouse IgG2a monoclonal antibody (manufactured by BD Pharmingen) and 95 μ l of PBS supplemented with 0.1% fetal bovine serum, and left to stand on ice for 1 hour. After washing the cells with PBS, fluorescence intensity was measured by FACSCalibur manufactured by Beckton Dickinson. On the other hand, the same operation as described above was carried out to prepare the cells as a control, using mouse IgG2a Isotype control (manufactured by MBL) instead of the mouse anti-human CD 179b antibody. As a result, the cells to which the anti-human CD179b antibody was added showed a fluorescence intensity not less than 10% higher than that of the control, and therefore it was confirmed that the CD 179b protein is expressed on the cell membrane surface of the above human cancer cell line.

Example 2: Anti-tumor Effect, against Cancer Cells, of the Antibody against CD 179b

(1) The ADCC Activity

[0122] Thereafter, whether or not the antibody against CD 179b can damage tumor cells expressing CD179b was studied. The evaluation was carried out using a commercially available mouse antibody against human CD179b (clone name: GA170). Into a 50 ml centrifuge tube, 10^6 cells belonging to each of the 3 types of human leukemia cells, Namalwa, BDCM and RPMI1788 (all of these were purchased from ATCC), whose expression of CD 179b was confirmed in Example 1(5), were collected, and 100 μ Ci of chromium 51 was added to the tube, followed by incubation at 37°C for 2 hours. Thereafter, the cells were washed 3 times with RPMI medium supplemented with 10% fetal calf serum, and placed in a 96-well V-bottom plate in an amount of 10^3 cells/well. To each well, 1 μ g of GA170 was added, and 2×10^5 lymphocytes separated from mouse spleen were further added thereto, followed by culture under the conditions of 37°C, 5% CO₂ for 4 hours. Thereafter, the amount of chromium 51 in the culture supernatant released from damaged tumor cells was measured, and the ADCC activity by GA170 against each type of cancer cells was calculated. As a result, ADCC activities of 32.6%, 32.3% and 28.3% were confirmed for Namalwa, BDCM and RPMI1788, respectively. On the other hand, when an isotype control (clone name: 6H3) of GA170 was used for the same operation, the above activity was not detected. Thus, it was revealed that, by the ADCC activity induced using an antibody against GD179b, tumor cells expressing CD 179b can be damaged.

[0123] The cytotoxic activity was obtained as a result of a process wherein the antibody against CD179b used in the present invention, mouse lymphocytes, and 10^3 cells of each leukemia cell line were mixed together, followed by culturing the cells for 4 hours, measuring the amount of chromium 51 released into the medium after the culture, and calculating the cytotoxic activity against the leukemia cell line according to the following calculation equation*.

$$\begin{aligned} & \text{*Equation: Cytotoxic activity (\%)} = \frac{\text{the amount of chromium 51 released}}{\text{from Namalwa, BDCM or RPMI1788 upon addition of the antibody against CD179b}} \\ & \quad \times \frac{\text{and mouse lymphocytes / the amount of chromium 51 released from the target cells}}{\text{upon addition of 1N hydrochloric acid}} \times 100. \end{aligned}$$

(2) The CDC Activity

[0124] Blood collected from a rabbit was placed in an Eppendorf tube, and left to stand at room temperature for 60 minutes, followed by centrifugation at 3000 rpm for 5 minutes to prepare serum for measurement of the CDC activity. Into a 50 ml centrifuge tube, 10^6 cells belonging to each of the 3 types of human leukemia cells, Namalwa, BDCM and RPMI1788 were collected, and 100 μ Ci of chromium 51 was added to the tube, followed by incubation at 37°C for 2 hours and washing the cells 3 times with RPMI medium supplemented with 10% fetal calf serum. Thereafter, the cells were suspended in RPMI medium containing the rabbit serum prepared as above in an amount of 50%, and placed in a 96-well V-bottom plate in an amount of 10^3 cells/well. To each well, 1 μ g of GA170 was added, followed by culture under the conditions of 37°C, 5% CO₂ for 4 hours. Thereafter, the amount of chromium 51 in the culture supernatant released from damaged tumor cells was measured, and the CDC activity by GA170 against each cancer cells was calculated. As a result, CDC activities of 30.5%, 21.2% and 30.5% were confirmed for Namalwa, BDCM and RPMI1788, respectively. On the other hand, when an isotype control (clone name: 6H3) of GA170 was used for the same operation, the above activity was not detected. Thus, it was revealed that, by the CDC activity induced using an antibody against CD 179b, tumor cells expressing CD 179b can be damaged.

[0125] The cytotoxic activity was obtained, as in the above (1), as a result of calculation of the cytotoxic activity against each leukemia cell line according to the following calculation equation*.

$$\begin{aligned} & \text{*Equation: Cytotoxic activity (\%)} = \frac{\text{the amount of chromium 51 released}}{\text{from Namalwa, BDCM or RPMI1788 upon addition of the antibody against CD179b,}} \\ & \quad \times \frac{\text{and rabbit serum / the amount of chromium 51 released from the target cells upon}}{\text{addition of 1N hydrochloric acid}} \times 100. \end{aligned}$$

Example 3: Preparation of a Monoclonal Antibody

(1) Preparation of an Antigen Protein

[0126] The human CD179b protein was prepared by the method of lipofection to animal cells. The human CD179b gene (SEQ ID NO:22) was introduced to a vector encoding the human IgG1Fc region, the SRaIgG1Fc vector, via restriction sites *Xho*I and *Bam*HI. The SRaIgG1Fc vector is a vector prepared by introduction of the gene for the human IgG1Fc region into the pcDL-SRa296 vector (manufactured by DNAX). Subsequently, 24 µg of the plasmid was mixed with 60 µl of Lipofectamine 2000 (manufactured by Invitrogen), and OPTI-MEM (manufactured by Invitrogen) was added to the resulting mixture to attain a total volume of 3 ml, followed by leaving the mixture to stand at room temperature for not less than 20 minutes. To CHO-K1 cells preliminarily prepared to 2×10^6 cells/12 ml OPTI-MEM, 3 ml of the above-mentioned mixed solution of the plasmid was added, followed by 8 hours of culture under the conditions of 37°C and 5% CO₂. The medium was replaced with 10 ml of CHO-S-SFM medium (manufactured by Invitrogen), and culture was then carried out for 4 to 5 days. Purification of the antigen protein produced in the obtained culture supernatant was carried out using ProteinA sepharose HP (manufactured by GE Healthcare). ProteinA sepharose HP was sufficiently equilibrated with 20 mM phosphate buffer (pH 7.4)/0.15 M NaCl (equilibration buffer/washing buffer), and a solution prepared by mixing the culture supernatant with the equilibration buffer at a ratio of 1:1 was introduced thereto. Subsequently, the column was washed sufficiently with the washing buffer, and elution was carried out with 0.2 M Glycine buffer (pH 2.5). The eluted solution was neutralized by addition of 1 M Tris (pH 9), and the buffer was exchanged by ultrafiltration using 20 mM phosphate buffer (pH 7.4)/0.15 M NaCl, to prepare the human CD179b protein.

(2) Obtaining Hybridomas

[0127] With an equal amount of the MPL+TDM adjuvant (manufactured by Sigma), 100 µg of the antigen protein (human CD179b protein) prepared in (1) was mixed, to prepare an antigen solution for each individual of mouse. The antigen solution was intraperitoneally administered to a Balb/c mouse (Japan SLC, Inc.) of 6 weeks old, and 3 more times of administrations were then carried out at intervals of 1 week, thereby completing immunization. Spleen removed 3 days after the last immunization was placed between 2 sterile slide glasses and ground, followed by repeating 3 times of operations wherein the cells were washed with PBS(-) (manufactured by Nissui Pharmaceutical Co., Ltd.) and centrifuged at 1500 rpm for 10 minutes to remove the supernatant, thereby obtaining spleen cells. The obtained spleen cells and mouse myeloma cells SP2/0 (purchased from ATCC) were mixed together at a ratio of 10:1, and a PEG solution warmed to 37°C prepared by mixing 200 µl of RPMI1640 medium supplemented with 10% fetal calf serum and 800 µl of PEG1500 (manufactured by Boehringer) together was added to the resulting mixture, followed by leaving the mixture to stand for 5 minutes, thereby carrying out cell fusion. The supernatant was removed by 5 minutes of centrifugation at 1700 rpm, and the cells were suspended in 150 ml of RPMI1640 medium (HAT selection medium) supplemented with 15% fetal calf serum, to which 2% equivalent of HAT solution manufactured by Gibco was added. On each well of 15 96-well plates (manufactured by Nunc), 100 µl of the cell suspension was seeded. The cells were cultured for 7 days under the environment of 37°C, 5%CO₂, to obtain hybridomas produced by fusion of the spleen cells and the myeloma cells.

(3) Selection of the Hybridomas

[0128] Using as indices the binding affinities, against the human CD 179b protein, of the antibodies produced by the prepared hybridomas, hybridomas were selected. In each well of a 96-well plate, 100 µl of 1 µg/ml solution of the human CD179b protein prepared in the above (1) was placed, and the solution was left to stand at 4°C for 18 hours. Each well was washed with PBS-T 3 times, and 400 µl of 0.5% BSA (Bovine Serum Albumin) solution (manufactured by Sigma) was added to each well, followed by leaving the plate to stand at room temperature for 3 hours. The solution was removed, and the wells were washed 3 times with 400 µl/well of PBS-T, followed by adding 100 µl/well of the culture supernatant of each of the hybridomas obtained in the above (2) and leaving the plate at room temperature for 2 hours. After washing the wells 3 times with PBS-T, 100 µl of an HRP-labeled anti-mouse IgG (H+L) antibody (manufactured by Invitrogen) 5000-fold diluted with PBS was added to each well, and the plate was left to stand at room temperature for 1 hour. The wells were washed 3 times with PBS-T, and 100 µl of TMB substrate solution (manufactured by Thermo) was added to each well, followed by leaving the plate to stand for 15 to 30 minutes to carry out coloring reaction. After allowing coloration, 100 µl of 1 N sulfuric acid was added to each well to stop the reaction, and the absorbance at 450 nm to 595 nm was measured using an absorption spectrometer. As a result, hybridomas producing the antibodies showing the highest absorbance was selected.

[0129] The selected hybridomas were placed in a 96-well plate such that each well contains 0.5 cell, and cultured. One week later, hybridomas forming single colonies in the wells were observed. The cells in these wells were further

cultured to obtain 60 cloned hybridoma cell lines.

[0130] Subsequently, a hybridoma cell line was selected using as indices the binding affinities, against leukemia cells, of the antibodies produced by the above 60 hybridoma cell lines. In each well of a 96-well plate, 100 μ l of 1 mg/ml poly-L-lysine (manufactured by Sigma)-PBS solution was placed, and the plate was left to stand at room temperature for 30 minutes. After removing the poly-L-lysine-PBS solution, an operation of filling sterile distilled water in each well and discarding it was repeated 3 times, followed by air-drying of the plate in a clean bench. Namalwa, a human leukemia cell line for which expression of CD 179b was confirmed was suspended in PBS(-) such that a cell density of 10^6 cells/ml was attained, and 100 μ l of the resulting suspension was added to each well of the above plate, followed by leaving the plate to stand at room temperature for 15 minutes. After centrifugation at 1700 rpm for 5 minutes, the supernatant was removed, and 100 μ l of 0.05% glutaraldehyde (manufactured by Sigma)-PBS solution was added to each well, followed by leaving the plate to stand at room temperature for 10 minutes. Each well was washed with PBS-T 3 times, and 300 μ l of 0.5% BSA solution was added to each well, followed by leaving the plate to stand at 4°C for 18 hours. After washing the wells 3 times with PBS-T, 100 μ l of the culture supernatant of each of the 60 hybridoma cell lines obtained as above was added to the well, and the plate was left to stand at room temperature for 2 hours. The supernatant was removed and the wells were washed 3 times with PBS-T, followed by adding 100 μ l of an HRP-labeled anti-mouse IgG (H+L) antibody 5000-fold diluted with PBS to each well and leaving the plate to stand at room temperature for 1 hour. The wells were washed 3 times with PBS-T, and 100 μ l of TMB substrate solution (manufactured by Thermo) was added to each well, followed by leaving the plate to stand for 30 minutes to carry out coloring reaction. After allowing coloration, 100 μ l of 1 N sulfuric acid was added to each well to stop the reaction, and the absorbance at 450 nm to 595 nm was measured using an absorption spectrometer. As a result, the hybridoma cell line #8, which produces the antibody showing the highest absorbance, was selected.

[0131] The isotype of the anti-CD 179b monoclonal antibody #8 produced by the hybridoma cell strain #8 selected as described above was determined by the ELISA method. The culture supernatant of the hybridoma cell strain #8 was evaluated with the sub-isotyping kit (COSMO BIO Co., Ltd.) according to the protocols described in the attached instructions, and, as a result, the anti-CD179b monoclonal antibody was revealed to be IgG3.

Example 4: The Anti-tumor Effect of the Anti-CD179b Monoclonal Antibody #8

(1) Preparation of the Anti-CD179b Monoclonal Antibody #8

[0132] The hybridoma cell strain #8 was cultured in Hybridoma SFM (manufactured by Invitrogen). The culture fluid was centrifuged at 1500 rpm for 10 minutes, and passed through a filter system 0.22 μ m. For purification of the antibody, a Hitrap Protein A Sepharose FF (manufactured by GE Healthcare) column was used. The column was washed with PBS for equilibration. Subsequently, the culture supernatant was introduced to the column, followed by washing the column with PBS. Elution was carried out with 0.1M Glycine-HCl (pH2.5) to obtain a purified antibody.

The Anti-tumor Effect in Vitro (on Cells)

The ADCC Activity

[0133] Whether or not the anti-CD179b monoclonal antibody #8 can damage tumor cells expressing human CD 179b was studied. Human leukemia cells Namalwa, for which expression of human CD179b was confirmed, were collected into a 50 ml centrifuge tube in an amount of 10^6 cells, and 10 μ Ci of chromium 51 was added to the tube, followed by incubation at 37°C for 2 hours. Thereafter, the cells were washed 3 times with RPMI medium supplemented with 10% fetal calf serum, and placed in a 96-well V-bottom plate in an amount of 10^3 cells/well. To each well, 2 μ g of the anti-CD 179b monoclonal antibody #8 was added, and 2×10^5 lymphocytes separated from mouse spleen were further added thereto, followed by culture under the conditions of 37°C, 5% CO₂ for 4 hours. Thereafter, the amount of chromium 51 in the culture supernatant released from damaged tumor cells was measured, and the ADCC activity by the anti-CD179b monoclonal antibody #8 against the Namalwa cells was calculated. As a result, an ADCC activity of 60.6% was confirmed for Namalwa in each well. On the other hand, when an isotype control (clone name: ME07) was used in a similar operation, the above activity was not detected. Thus, it was revealed that the anti-CD 179 monoclonal antibody #8 can damage tumor cells expressing CD179b by its ADCC activity.

The CDC Activity

[0134] Blood collected from a rabbit was placed in an Eppendorf tube, and left to stand at room temperature for 60 minutes, followed by centrifugation at 3000 rpm for 5 minutes to prepare serum for measurement of the CDC activity. Into a 50 ml centrifuge tube, 10^6 cells of Namalwa, which are human leukemia cells, were collected, and 100 μ Ci of

chromium 51 was added to the tube, followed by incubation at 37°C for 2 hours and washing the cells 3 times with RPMI medium supplemented with 10% fetal calf serum. Thereafter, the cells were suspended in RPMI medium containing the rabbit serum prepared as described above in an amount of 50%, and placed in a 96-well V-bottom plate in an amount of 10^3 cells/well. To each well, 2 µg of the anti-CD179b monoclonal antibody #8 was added, followed by culture under the conditions of 37°C, 5% CO₂ for 4 hours. Thereafter, the amount of chromium 51 in the culture supernatant released from damaged tumor cells was measured, and the CDC activity by the anti-CD 179b monoclonal antibody #8 against the Namalwa cells was calculated. As a result, a CDC activity of 30.5% was confirmed for Namalwa. On the other hand, when an isotype control (clone name: ME07) was used in a similar operation, the above activity was not detected. Thus, it was revealed that the anti-CD179b monoclonal antibody #8 can damage tumor cells expressing CD179b by its CDC activity.

(3) The Anti-tumor Effect in the Living Body of a Mouse

[0135] The anti-tumor activity of the anti-CD 179b monoclonal antibody #8 in the living body of a tumor-bearing mouse was evaluated. The antibody used was prepared by purifying the culture supernatant of the hybridoma cell strain #8 by a column in the same manner as described above.

[0136] Using a tumor-bearing mouse to which a cancer cell line derived from human which expresses CD 179b was transplanted, the anti-tumor activity of the anti-CD179b monoclonal antibody #8 was evaluated. The Namalwa cells were subcutaneously transplanted to the back of each of 20 nude mice (BALB/c Slc-nu/nu, derived from Japan SLC, Inc.) in an amount of 10^6 cells, and the tumor was allowed to grow to a size of about 7 mm in diameter. Among these mice, each of 10 tumor-bearing mice was subjected to administration of 10^7 lymphocytes separated from peripheral blood of BALB/c mice (BALB/c Cr Slc, derived from Japan SLC, Inc.) and 300 µg of the anti-CD 179b monoclonal antibody #8 from a caudal vein. Thereafter, the same amounts of the mouse lymphocytes and the antibody were administered to each tumor-bearing mouse from a caudal vein a total of 3 times in 2 days, and the size of the tumor was measured every day, thereby evaluating the anti-tumor effect. On the other hand, to each of the remaining 10 tumor-bearing mice, PBS(-) was administered instead of the above antibody, to provide a control group. As a result of this study, in the group wherein the anti-CD 179b antibody was administered, the tumor volume reduced to 65% on Day 8 with respect to the tumor volume at the beginning of the administration of the antibody, which was defined as 100%. On Day 11, Day 17 and Day 20, the tumor regressed to 52%, 45% and 35%, respectively (see Fig. 2). On the other hand, in the control group, on Day 8, Day 11, Day 17 and Day 20, the tumor grew to about 180%, 220%, 350% and 420% (see Fig. 2). From these results, it was shown that the obtained anti-CD 179b monoclonal antibody #8 exerts a strong anti-tumor effect in the living body, against cancer cells expressing CD179b. In terms of the size of the tumor, the volume was calculated using the calculation equation: longer diameter×shorter diameter×shorter diameter×0.5.

Example 5: Cloning of the Gene for the Variable Region of the Anti-CD179b Monoclonal Antibody #8

[0137] From the hybridoma cell line #8, mRNA was extracted, and the genes for the heavy chain variable (VH) region and the light chain variable (VL) region of the anti-CD179b monoclonal antibody #8 were obtained by the RT-PCR method using primers specific to a mouse leader sequence and the antibody constant region of IgG3. For determination of their sequences, these genes were cloned into the pCR2.1 vector (manufactured by Invitrogen).

(1) RT-PCR

[0138] From 10^6 cells of the hybridoma cell strain #8, mRNA was prepared using the mRNA micro purification kit (manufactured by GE Healthcare), and the obtained mRNA was reverse-transcribed to synthesize cDNA using the SuperScript II 1st strand synthesis kit (manufactured by Invitrogen). These operations were carried out according to the protocols described in the attached instructions of the respective kits.

[0139] Using the obtained cDNA, the antibody genes were amplified by the PCR method. To obtain the gene for the VH region, a primer specific to the mouse leader sequence (SEQ ID NO:112) and a primer specific to the mouse IgG3 constant region (SEQ ID NO:113) were used. Further, to obtain the gene for the VL region, a primer specific to the mouse leader sequence (SEQ ID NO:114) and a primer specific to the mouse κ chain constant region (SEQ ID NO:115) were used. These primers were designed referring to Jones ST and Bending MM Bio/technology 9, 88-89 (1991). For the PCR, Ex Taq (manufactured by TAKARA BIO INC.) was used. To 5 µl of 10×EX Taq Buffer, 4 µl of dNTP Mixture (2.5 mM), 2 µl each of the primers (1.0 µM) and 0.25 µl of Ex Taq (5 units/ µl), a cDNA sample was added, and sterile water was added to the resulting mixture to a total volume of 50 µl. The reaction was carried out under the conditions of 2 minutes of treatment at 94°C followed by 30 cycles of the combination of denaturation at 94°C for 1 minute, annealing at 58°C for 30 seconds and the extension reaction at 72°C for 1 minute.

(2) Cloning

[0140] Using each of the PCR products obtained as described above, electrophoresis was carried out with agarose gel, and the DNA band corresponding to each of the VH region and the VL region was excised. Each DNA fragment was processed using the QIAquick Gel purification kit (manufactured by QIAGEN) according to the protocol described in the attached instructions. Each purified DNA was cloned into the pCR2.1 vector using the TA cloning kit (manufactured by Invitrogen). The vector to which the DNA was linked was used for transformation of DH5a competent cells (manufactured by TOYOBO) according to a conventional method. Ten clones each of the transformants were cultured in a medium (100 µg/ml ampicillin) at 37°C overnight, and each plasmid DNA was purified using the Qiaspin Miniprep kit (manufactured by QIAGEN).

(3) Determination of the Sequences

[0141] The analysis of the gene sequences of the VH region and the VL region was carried out by analyzing the plasmid DNAs in (2) using the M13 forward primer (SEQ ID NO:116) and the M13 reverse primer (SEQ ID NO:117), by a fluorescent sequencer (DNA sequencer 3130XL manufactured by ABI), using the BigDye Terminator Ver. 3.1 Cycle Sequencing kit according to the protocol in the attached instructions. As a result, the respective gene sequences were determined (identical among the 10 clones for each gene). The amino acid sequence of the VH region of the anti-CD179b monoclonal antibody #8 is shown in SEQ ID NO:105, and the amino acid sequence of the VL region of the antibody is shown in SEQ ID NO:109.

INDUSTRIAL APPLICABILITY

[0142] The antibody of the present invention is useful for therapy and/or prophylaxis of cancer.

SEQUENCE LISTING FREE TEXT

[0143]

SEQ ID NOs:94, 96 to 99: primers
SEQ ID NO:95: T7 primer
SEQ ID NOs:100 and 101: GAPDH primers
SEQ ID NOs:116 and 117: primers

SEQUENCE LISTING

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	Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val	
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	Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr	
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	Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu	
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	Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu	
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	Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu	
	145 150 155 160	
50	tgc tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct	530
	Cys Ser	
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10	Tyr	Tyr	Cys	Ser	Ser	Trp	Asp	Lys	Gly	Leu	Ser	Arg	Ser	Val	Phe	Gly	
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	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	
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	Tyr Tyr Cys Ala Leu Gly Leu Ser Ser Ser Ser Ser His Ser Val Phe	
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	Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro	
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	Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys	
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	Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr	
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	Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr	
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	Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr	
	100 105 110	
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	Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys	
	115 120 125	
40	ctg gtc aca cac gag ggg agc acc gtg gag aag aag gtg gcc ccc gca	433
	Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala	
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	Glu Cys Ser	
	145	
50	caggacctcc aggaggatct tgcctcctat ctgggtcatc ccgcccttct cccacacccc	545
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10	Gly	Gly	Gly	Thr	His	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ser	Pro	
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	Ile	Ser	Cys	Thr	Gly	Ser	Ser	Ser	Asn	Ile	Gly	Gly	Asn	Asn	Val	Gly		
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	Trp	Tyr	Gln	Gln	Leu	Pro	Gly	Arg	Gly	Pro	Arg	Thr	Val	Ile	Phe	Thr		
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15	aca	cat	agt	cga	ccc	tcg	ggg	gtg	tcc	gat	cga	ttc	tct	gcc	tcc	aag	193	
	Thr	His	Ser	Arg	Pro	Ser	Gly	Val	Ser	Asp	Arg	Phe	Ser	Ala	Ser	Lys		
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	Glu	Ala	Asp	Tyr	Tyr	Cys	Ser	Thr	Trp	Asp	Asp	Ser	Leu	Ser	Ala	Ala		
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	Val	Phe	Gly	Gly	Gly	Thr	His	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ala		
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	Ser	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala		
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	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly		
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	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Pro	Val	Thr	Gln	Gly	Val		
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	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser		
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	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe		
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	Pro	Ala	Glu	Cys	Ser													
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210

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10	Trp Tyr Gln Gln Leu Pro Gly Arg Gly Pro Arg Thr Val Ile Phe Thr	
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15	Thr His Ser Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Ala Ser Lys	
	50 55 60	
20	Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp	
	65 70 75 80	
25	Glu Ala Asp Tyr Tyr Cys Ser Thr Trp Asp Asp Ser Leu Ser Ala Ala	
	85 90 95	
30	Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys Ala	
	100 105 110	
35	Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala	
	115 120 125	
40	Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly	
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	145 150 155 160	
50	Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser	
	165 170 175	
55	Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe	
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        Thr Ala Arg Ile Thr Cys Glu Gly Asp Ser Ile Gly Ser Lys Arg Val
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20      tac tgg tac caa cag aac ctg ggc cag gtc cct cta ctg att atc tat      145
        Tyr Trp Tyr Gln Gln Asn Leu Gly Gln Val Pro Leu Leu Ile Ile Tyr
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        Asp Asp Ala Thr Arg Pro Ser Arg Ile Pro Asp Arg Phe Ser Gly Ala
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30      aac tcg ggg gac aca gcc acc ctg acc atc agc ggg gcc ctg gcc gag      241
        Asn Ser Gly Asp Thr Ala Thr Leu Thr Ile Ser Gly Ala Leu Ala Glu
        65              70              75              80

35      gac gag gct gac tat tac tgt cag gtg tgg gac agt gat agt aag act      289
        Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp Ser Lys Thr
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40      ggt gta ttc ggc gga ggc acc cac ctg acc gtc ctc ggt cag ccc aag      337
        Gly Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys
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        Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly
              115              120              125

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

55      ggt gtg acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc      481
        Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly
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10 ttc agc tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg 625
Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val
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15 gcc ccc gca gag tgc tct tag gttcccgacg gccccgcca ccgaaggggg 676
Ala Pro Ala Glu Cys Ser
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Tyr Trp Tyr Gln Gln Asn Leu Gly Gln Val Pro Leu Leu Ile Ile Tyr
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Asp Asp Ala Thr Arg Pro Ser Arg Ile Pro Asp Arg Phe Ser Gly Ala
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Asn Ser Gly Asp Thr Ala Thr Leu Thr Ile Ser Gly Ala Leu Ala Glu
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5 Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Asp Ser Lys Thr
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10 Gly Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys
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Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly
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15 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser
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20 Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly
145 150 155 160

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

Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser
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	Thr Asn Ile Gly Ser Val Gly Ala Thr Trp Tyr Gln His Leu Pro Gly	
	50 55 60	
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	Lys Ala Pro Arg Leu Leu Leu Tyr Thr His Gly Glu Arg Pro Ser Gly	
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	Thr Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln	
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	130 135 140	
35	ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc	481
	Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys	
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	Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala	
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	Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys	
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	Thr Gly Ser Trp Ala Gln Ser Val Leu Thr His Pro Thr Ser Val Ser	
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10	ggg tcc ctt ggc cag agg gtc acc att tcc tgc tcc gga agc acg aac	145
	Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Asn	
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15	aac atc ggt act gtt ggt gcg ggc tgg tac caa cag ttc cca gga aag	193
	Asn Ile Gly Thr Val Gly Ala Gly Trp Tyr Gln Gln Phe Pro Gly Lys	
	50 55 60	
20	gcc cct aaa ctc ctc att tac agt gat ggg aat cga ccg tca ggg gtc	241
	Ala Pro Lys Leu Leu Ile Tyr Ser Asp Gly Asn Arg Pro Ser Gly Val	
	65 70 75 80	
25	cct gac cgg ttt tcc ggc tcc aag tca ggc aac tca gcc acc ctg acc	289
	Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Ser Ala Thr Leu Thr	
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30	atc att gga ctt cag gct gag gac gag gct gat tac tac tgt cag tct	337
	Ile Ile Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser	
	100 105 110	
35	gtt gat ccc acg ctt ggt ggt cat gtg ttc ggc gga ggc acc cat ctg	385
	Val Asp Pro Thr Leu Gly Gly His Val Phe Gly Gly Gly Thr His Leu	
	115 120 125	
40	acc gtc ctc ggt cag ccc aag gcc tcc cct tcg gtc aca ctc ttc ccg	433
	Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro	
	130 135 140	
45	ccc tcc tct gag gag ctt ggc gcc aac aag gcc acc ctg gtg tgc ctc	481
	Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu	
	145 150 155 160	
50	atc agc gac ttc tac ccc agc ggc gtg aca gtg gcc tgg aag gca gac	529
	Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp	
	165 170 175	
55	ggc agc ccc atc acc cag ggt gtg gag acc acc aag ccc tcc aag cag	577
	Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln	

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10	aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag ggg Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly 210 215 220	673		
15	agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser 225 230 235	715		
20	gttcctgatg tccccgccc accaaagggg gctcagagcc tcaggacctc caggaggatc ttgcctccca tctgggtcat ccagccttt ccccttaaac ccaggcaaca ttcaataaag tgttctttct tcaatcagaa aaaaaaaaaa aaaaaaaaaa	775 835 875		
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10	Gly	Ser	Leu	Gly	Gln	Arg	Val	Thr	Ile	Ser	Cys	Ser	Gly	Ser	Thr	Asn
			35					40					45			
15	Asn	Ile	Gly	Thr	Val	Gly	Ala	Gly	Trp	Tyr	Gln	Gln	Phe	Pro	Gly	Lys
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20	Ala	Pro	Lys	Leu	Leu	Ile	Tyr	Ser	Asp	Gly	Asn	Arg	Pro	Ser	Gly	Val
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25	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Ser	Ala	Thr	Leu	Thr
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30	Ile	Ile	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser
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35	Val	Asp	Pro	Thr	Leu	Gly	Gly	His	Val	Phe	Gly	Gly	Gly	Thr	His	Leu
			115					120					125			
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45				130				135					140			
50	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu
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55	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp
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60	Gly	Ser	Pro	Ile	Thr	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln
				180					185					190		
65	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp
			195					200					205			
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cac tgc aca ggg tcc tgg gcc cag tct atg ctg act cag ccg gcc tca	97
His Cys Thr Gly Ser Trp Ala Gln Ser Met Leu Thr Gln Pro Ala Ser	
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gtg tct ggg tcc ctg ggc cag aag gtc acc atc tcc tgc act gga agc	145
Val Ser Gly Ser Leu Gly Gln Lys Val Thr Ile Ser Cys Thr Gly Ser	
35 40 45	
agc tcc aac atc ggt gct tat tat gtg agc tgg tac caa cag tcc cca	193
Ser Ser Asn Ile Gly Ala Tyr Tyr Val Ser Trp Tyr Gln Gln Ser Pro	
50 55 60	
gga aaa ggc cct aga acc gtc atc tat ggt gat aat tac cga cct tca	241
Gly Lys Gly Pro Arg Thr Val Ile Tyr Gly Asp Asn Tyr Arg Pro Ser	
65 70 75 80	
ggg gtc ccc gat cga ttc tct ggc tcc aag tca ggc agt tca gcc acc	289
Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Ser Ser Ala Thr	
85 90 95	

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	Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Glu Tyr Tyr Cys	
	100 105 110	
5	tta tca tgg gat aat agt ctc aga ggt ggt gtg ttc ggc gga ggc acc	385
	Leu Ser Trp Asp Asn Ser Leu Arg Gly Gly Val Phe Gly Gly Gly Thr	
	115 120 125	
10	cac ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc	433
	His Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu	
	130 135 140	
15	ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg	481
	Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val	
	145 150 155 160	
	tgc ctc atc agc gac ttc tac ccc agc ggt gtg acg gtg gcc tgg aag	529
	Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys	
	165 170 175	
20	gca gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc	577
	Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser	
	180 185 190	
25	aag cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg	625
	Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr	
	195 200 205	
30	cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac	673
	Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His	
	210 215 220	
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	Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	225 230 235	
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	20 25 30	
	Val Ser Gly Ser Leu Gly Gln Lys Val Thr Ile Ser Cys Thr Gly Ser	
	35 40 45	

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5	Gly	Lys	Gly	Pro	Arg	Thr	Val	Ile	Tyr	Gly	Asp	Asn	Tyr	Arg	Pro	Ser
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15	Leu	Thr	Ile	Ser	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Glu	Tyr	Tyr	Cys
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			115					120					125			
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35	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Val	Thr	Val	Ala	Trp	Lys
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40	Ala	Asp	Gly	Ser	Pro	Val	Thr	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser
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45	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr
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	Leu Thr Leu Leu Ala His Cys Thr Gly Ser Trp Ala Gln Ser Val Leu	
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10	act cag ccg gcc tca gtg tct ggg tcc ctg ggc cag agg gtc acc atc	145
	Thr Gln Pro Ala Ser Val Ser Gly Ser Leu Gly Gln Arg Val Thr Ile	
	35 40 45	
15	tcc tgc act gga acc agc tcc aat atc ggt aca gat tat gtg ggc tgg	193
	Ser Cys Thr Gly Thr Ser Ser Asn Ile Gly Thr Asp Tyr Val Gly Trp	
	50 55 60	
20	tac caa cag ctc cca gga aga ggc ccc aga acc ctc atc tct gat act	241
	Tyr Gln Gln Leu Pro Gly Arg Gly Pro Arg Thr Leu Ile Ser Asp Thr	
	65 70 75 80	
25	agt cgc cga ccc tcg ggg gtc cct gat cga ttc tct ggc tcc agg tca	289
	Ser Arg Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser	
	85 90 95	
30	ggc acc aca gca atc ctg act atc tct ggg ctc cag gct gag gac gag	337
	Gly Thr Thr Ala Ile Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu	
	100 105 110	
35	gct gat tat tac tgc tca gca tat gac agc agt ctc ggt gga act atc	385
	Ala Asp Tyr Tyr Cys Ser Ala Tyr Asp Ser Ser Leu Gly Gly Thr Ile	
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40	ttc ggc gga ggc act ttc ctg acc gtc ctc ggt cag ccc aag gcc tcc	433
	Phe Gly Gly Gly Thr Phe Leu Thr Val Leu Gly Gln Pro Lys Ala Ser	
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	Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn	
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50	aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc ggc gtg	529
	Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val	
	165 170 175	
55	acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag	577
	Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu	
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60	acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc	625
	Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser	
	195 200 205	
65	tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc agc	673
	Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser	
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70	tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg gcc ccc	721
	Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro	
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75	gca gag tgc tct tag gttcccgacg gccccgccca ccgaaggggg cccggagcct	776

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Ala Glu Cys Ser

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10	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Leu	Gly	Gln	Arg	Val	Thr	Ile	
			35					40					45				
15	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asn	Ile	Gly	Thr	Asp	Tyr	Val	Gly	Trp	
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25	Ser	Arg	Arg	Pro	Ser	Gly	Val	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Arg	Ser	
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30	Gly	Thr	Thr	Ala	Ile	Leu	Thr	Ile	Ser	Gly	Leu	Gln	Ala	Glu	Asp	Glu	
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35	Ala	Asp	Tyr	Tyr	Cys	Ser	Ala	Tyr	Asp	Ser	Ser	Leu	Gly	Gly	Thr	Ile	
			115					120					125				
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	130						135					140					
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	145					150					155					160	
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5	Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser	
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	Arg Gly Pro Arg Thr Val Ile Tyr Ser Thr Asn Val Arg Pro Ser Gly	
	20 25 30	
35	gtg ccc gat cga ttc tct ggc tcc aag tct gac aac aca ggc acc ctg	145
	Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Asp Asn Thr Gly Thr Leu	
	35 40 45	
40	acc atc tct gga ctc cag gct gag gat gag gct gat tat tat tgc gca	193
	Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala	
	50 55 60	
	acg tgg gat gat agt ctc agt gtt tct ctg ttc ggc gga ggc acc cac	241
	Thr Trp Asp Asp Ser Leu Ser Val Ser Leu Phe Gly Gly Gly Thr His	
45	65 70 75 80	
	ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc	289
	Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe	
	85 90 95	
50	ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc	337
	Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys	
	100 105 110	
55	ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca	385
	Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala	
	115 120 125	

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

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

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

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

gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct 634

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

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

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

Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
 50 85 90 95

Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys
 55 100 105 110

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

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	Asp	Gly	Ser	Pro	Val	Thr	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys
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	145					150					155					160
10	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Glu
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	Leu Phe Ala His Cys Ala Gly Ser Trp Ala Gln Ser Val Leu Thr Gln	
	20 25 30	
10	ccg gcc tca gtg tct ggg tcc ctg ggc cag agg gtc acc atc tcc tgc	145
	Pro Ala Ser Val Ser Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys	
	35 40 45	
15	act gga agc agc tcc aat gtt ggt ttt ggc gat tat gtg ggc tgg tac	193
	Thr Gly Ser Ser Ser Asn Val Gly Phe Gly Asp Tyr Val Gly Trp Tyr	
	50 55 60	
20	cag cag ctc cca gga aga ggc ccc aga acc ctc ttc tac cgt gct act	241
	Gln Gln Leu Pro Gly Arg Gly Pro Arg Thr Leu Phe Tyr Arg Ala Thr	
	65 70 75 80	
25	ggc cga ccc tcg ggg gtc cct gat cga ttc tct gcc tcc agg tca ggc	289
	Gly Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Ala Ser Arg Ser Gly	
	85 90 95	
30	acc aca gcg acc ctg acc atc tct gga ctc cag cct gag gat gaa gcc	337
	Thr Thr Ala Thr Leu Thr Ile Ser Gly Leu Gln Pro Glu Asp Glu Ala	
	100 105 110	
35	gat tat tac tgc tca tcc tat gac tct act ctc ttt tct gtg ttc ggc	385
	Asp Tyr Tyr Cys Ser Ser Tyr Asp Ser Thr Leu Phe Ser Val Phe Gly	
	115 120 125	
40	gga ggc acc tac ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg	433
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50		
55		

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	Gly	Gly	Thr	Tyr	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ser	Pro	Ser	
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	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	
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	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Pro	Val	Thr	Gln	Gly	Val	Glu	Thr	Thr	
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	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	
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	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	
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	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Lys	Val	Ala	Pro	Ala	Glu	
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	Cys	Ser															
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	Gly Asn Tyr Val Gly Trp Tyr Gln Gln Leu Pro Gly Thr Gly Pro Arg	
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	Thr Leu Ile Tyr Gly Lys Asn His Arg Pro Ala Gly Val Pro Asp Arg	
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	Phe Ser Gly Ser Thr Ser Gly Ser Ser Ala Thr Leu Thr Ile Ser Gly	
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	Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile	
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	85 90 95	
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	Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser	
	100 105 110	
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	Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp	
	115 120 125	
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	Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro	
	130 135 140	
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	Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn	
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	Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys	
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	Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val	
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	Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
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Thr Leu Ile Tyr Gly Lys Asn His Arg Pro Ala Gly Val Pro Asp Arg
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Phe Ser Gly Ser Thr Ser Gly Ser Ser Ala Thr Leu Thr Ile Ser Gly
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Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
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Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
115 120 125

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

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

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Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys
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	Ile Thr Cys Glu Gly Asp Ser Ile Gly Asp Lys Arg Val Tyr Trp Tyr	
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	Gln Gln Lys Leu Gly Arg Gly Pro Met Leu Ile Ile Tyr Asp Gly Thr	
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	Gly Thr Arg Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val	
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	130 135 140	
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	Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys	
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65	ccc tcc aag cag agc aac aac aag tac gcg gcc agc agc tac ctg agc	576
	Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser	
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	Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys	
	210 215 220	
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	Ser	
	225	
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	Trp Tyr Gln Gln Leu Pro Gly Arg Gly Pro Lys Thr Val Val Ser Asn	
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	Thr Asn Ile Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Ala Ser Lys	
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	Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly	
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	Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser Phe	
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	Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val Ala	
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	Pro Ala Glu Cys Ser	
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5	Met Phe Gly Ser Gly Thr Gln Leu Thr Val Leu Gly Gln Pro Lys Ala	
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	115 120 125	
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	145 150 155 160	
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	Leu Pro Gly Thr Ser Pro Arg Asn Leu Ile Tyr Asp Thr Ser Ser Arg	
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	Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Arg Ser Gly Ser Thr	
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	Tyr Cys Ser Ser Tyr Asp Arg Ser Leu Ser Gly Ala Val Phe Gly Gly	
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	Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala	
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35	tgg aag gca gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag	624
	Trp Lys Ala Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys	
	195 200 205	
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	Ala	His	Ile	Thr	Cys	Gly	Gly	Asp	Asn	Ile	Gly	Ser	Lys	Tyr	Val	Gln	
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	Trp	Ile	Gln	Gln	Asn	Pro	Gly	Gln	Ala	Pro	Val	Val	Ile	Ile	Tyr	Arg	
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	Asp	Thr	Lys	Arg	Pro	Thr	Trp	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ala	Asn	
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	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	Thr	Asp	Ser	Gly	Pro	Gln	Thr	Asn	
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	Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser	
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15	agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc ttc	626
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   Thr Gly Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Thr Ser Val Ser
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   Gly Ser Leu Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Asn
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15	atc	act	ggg	ctt	cag	gct	gag	gac	gag	gct	gat	tat	tac	tgc	cag	tcc	337
	Ile	Thr	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	
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	Phe	Asp	Thr	Thr	Leu	Gly	Ala	Val	Phe	Gly	Gly	Gly	Thr	His	Leu	Thr	
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	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ser	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	
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	Thr	Val	Glu	Lys	Lys	Val	Ala	Pro	Ala	Glu	Cys	Ser					
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10	Gly	Ser	Leu	Gly	Gln	Arg	Val	Thr	Ile	Ser	Cys	Ser	Gly	Ser	Thr	Asn	
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30	Ile	Thr	Gly	Leu	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	
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40	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ser	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	
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	Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe	
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	Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys	
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25	ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca	192
	Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala	
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	Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys	
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	Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro	
	85 90 95	
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	Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
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	Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys	
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15	ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca	192
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	Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys	
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25	cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct	288
	Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro	
	85 90 95	
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EP 2 305 300 B1

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	Phe Lys Ala Val Ser Leu Cys Tyr Val Phe Gly Ser Gly Thr Gln Leu	
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	Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro	
	35 40 45	
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	Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu	
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20	atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca gac	240
	Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp	
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25	ggc agc ccc atc acc cag ggc gtg gag acc acc aag ccc tcc aag cag	288
	Gly Ser Pro Ile Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln	
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30	agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac	336
	Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp	
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	Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly	
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20	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	
				100					105					110			
25	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Glu	Gly	
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30	Ser	Thr	Val	Glu	Lys	Lys	Val	Ala	Pro	Ala	Glu	Cys	Ser				
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	Met	Phe	Glu	Ala	Val	Ser	Gln	Cys	Ala	Val	Phe	Gly	Gly	Gly	Thr	His	
	1				5					10					15		
45	ctg	acc	gtc	ctc	ggg	cag	ccc	aag	gcc	tcc	ccc	tcg	gtc	aca	ctc	ttc	96
	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ser	Pro	Ser	Val	Thr	Leu	Phe	
				20					25				30				
50	ccg	ccc	tcc	tct	gag	gag	ctc	ggc	gcc	aac	aag	gcc	acc	ctg	gtg	tgc	144
	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	
			35					40					45				
55	ctc	atc	agc	gac	ttc	tac	ccc	agc	ggc	gtg	acg	gtg	gcc	tgg	aag	gca	192
	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Val	Thr	Val	Ala	Trp	Lys	Ala	
		50					55					60					
60	gac	ggc	agc	ccc	gtc	acc	cag	ggc	gtg	gag	acc	acc	aag	ccc	tcc	aag	240
	Asp	Gly	Ser	Pro	Val	Thr	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	
	65					70					75					80	

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

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

gttcccgacg gccccgccca cctaaggggg cccggagcct caggacctcc aggaggatct 441

15 tgcctcccat ctgggtcatc ccgtcttctt ccccgacccc aggcagcact caataaagtg 501

ttctttgttc aat 514

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

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

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

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

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

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

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EP 2 305 300 B1

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15	ctg acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc	96
	Leu Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe	
	20 25 30	
20	ccg ccc tcc tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc	144
	Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys	
	35 40 45	
25	ctc atc agc gac ttc tac ccc agc ggc gtg acg gtg gcc tgg aag gca	192
	Leu Ile Ser Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala	
	50 55 60	
30	gac ggc agc ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag	240
	Asp Gly Ser Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys	
	65 70 75 80	
35	cag agc aac aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct	288
	Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro	
	85 90 95	
40	gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag	336
	Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu	
	100 105 110	
45	ggg agc acc gtg gag aag aag gtg gcc ccc gca gag tgc tct tag	381
	Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	115 120 125	
50	gttcccgacg gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct	441
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5	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ser	Pro	Ser	Val	Thr	Leu	Phe
				20					25					30		
	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys
10			35					40					45			
	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Val	Thr	Val	Ala	Trp	Lys	Ala
	50						55					60				
15	Asp	Gly	Ser	Pro	Val	Thr	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys
	65					70					75					80
	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro
20					85					90					95	
	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Glu
25				100					105					110		
	Gly	Ser	Thr	Val	Glu	Lys	Lys	Val	Ala	Pro	Ala	Glu	Cys	Ser		
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EP 2 305 300 B1

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5	gaa tgg tgg gct act ctc aga aat gat cgg gaa aag ctg gag gat ggg	96
	Glu Trp Trp Ala Thr Leu Arg Asn Asp Arg Glu Lys Leu Glu Asp Gly	
	20 25 30	
10	act ctc aga atc cca cgg tgg cac atg aac aaa tac cta gtc acg aca	144
	Thr Leu Arg Ile Pro Arg Trp His Met Asn Lys Tyr Leu Val Thr Thr	
	35 40 45	
15	gtc ccc gta gag cca gcc agt ctc aaa gag gtg gcc agg aag att ccg	192
	Val Pro Val Glu Pro Ala Ser Leu Lys Glu Val Ala Arg Lys Ile Pro	
	50 55 60	
20	atc cat gat gaa tgt ggt gtg ttc ggc gga ggc acc cac ctg acc gtc	240
	Ile His Asp Glu Cys Gly Val Phe Gly Gly Gly Thr His Leu Thr Val	
	65 70 75 80	
25	ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg ccc tcc	288
	Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser	
	85 90 95	
30	tct gag gag ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc atc agc	336
	Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser	
	100 105 110	
35	gac ttc tac ccc agc ggt gtg acg gtg gcc tgg aag gca gac ggc agc	384
	Asp Phe Tyr Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser	
	115 120 125	
40	ccc gtc acc cag ggc gtg gag acc acc aag ccc tcc aag cag agc aac	432
	Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn	
	130 135 140	
45	aac aag tac gcg gcc agc agc tac ctg agc ctg acg cct gac aag tgg	480
	Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp	
	145 150 155 160	
50	aaa tct cac agc agc ttc agc tgc ctg gtc acg cac gag ggg agc acc	528
	Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr	
	165 170 175	
55	gtg gag aag aag gtg gcc ccc gca gag tgc tct tag gttcccgacg	574
	Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	180 185	
60	gccccgccca ccgaaggggg cccggagcct caggacctcc aggaggatct tgcctcccat	634
	ctgggtcatc ccgcccttct ccccgacccc aggcagcact caataaagtg ttctttgttc	694
	aat	697
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<213> Canis familiaris

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      20          25          30

15     Thr Leu Arg Ile Pro Arg Trp His Met Asn Lys Tyr Leu Val Thr Thr
      35          40          45

20     Val Pro Val Glu Pro Ala Ser Leu Lys Glu Val Ala Arg Lys Ile Pro
      50          55          60

25     Ile His Asp Glu Cys Gly Val Phe Gly Gly Gly Thr His Leu Thr Val
      65          70          75          80

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

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

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

45     Pro Val Thr Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn
      130         135         140

50     Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp
      145         150         155         160

55     Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr
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      Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser
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EP 2 305 300 B1

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	1 5 10 15	
10	ccc ccc ttc aac ccg acc agt acc cgt gac aag ggg gct gcc ctt tgg	96
	Pro Pro Phe Asn Pro Thr Ser Thr Arg Asp Lys Gly Ala Ala Leu Trp	
	20 25 30	
15	gcc tcc cga gca gct gca ggg ttt gtg ctc gag gct gtg tca cag tgt	144
	Ala Ser Arg Ala Ala Ala Gly Phe Val Leu Glu Ala Val Ser Gln Cys	
	35 40 45	
20	att gtg ttc ggc gga ggc acc cat ctg acc gtc ctc ggt cag ccc aag	192
	Ile Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys	
	50 55 60	
25	gcc tcc cct tcg gtc aca ctc ttc ccg ccc tcc tct gag gag ctt ggc	240
	Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gly	
	65 70 75 80	
30	gcc aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac ccc agc	288
	Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Ser	
	85 90 95	
35	ggc gtg aca gtg gcc tgg aag gca gac ggc agc ccc atc acc cag ggt	336
	Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Ile Thr Gln Gly	
	100 105 110	
40	gtg gag acc acc aag ccc tcc aag cag agc aac aac aag tac gcg gcc	384
	Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala	
	115 120 125	
45	agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac agc agc	432
	Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His Ser Ser	
	130 135 140	
50	ttc agc tgc ctg gtc acg cac gag ggg agc acc gtg gag aag aag gtg	480
	Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val	
	145 150 155 160	
55	gcc ccc gca gag tgc tct tag gttcctgatg tcccccgccc accaaagggg	531
	Ala Pro Ala Glu Cys Ser	
	165	
	gctcagagcc tcaggacctc caggaggatc ttgcctccca tctgggtcat cccagccttt	591
	ccccttaaac ccaggcaaca ttcaataaag tgttctttct tca	634
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EP 2 305 300 B1

<213> Canis familiaris

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10     Pro Pro Phe Asn Pro Thr Ser Thr Arg Asp Lys Gly Ala Ala Leu Trp
      20          25          30

15     Ala Ser Arg Ala Ala Ala Gly Phe Val Leu Glu Ala Val Ser Gln Cys
      35          40          45

20     Ile Val Phe Gly Gly Gly Thr His Leu Thr Val Leu Gly Gln Pro Lys
      50          55          60

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

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

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

40     Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
      115         120         125

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

50     Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys Lys Val
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55     Ala Pro Ala Glu Cys Ser
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5	caa caa aca tct gcc ttg acc cgc tgt cct tcc atc ccc aca ggt cag	104
	Gln Gln Thr Ser Ala Leu Thr Arg Cys Pro Ser Ile Pro Thr Gly Gln	
	10 15 20	
10	ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg ccc tcc tct gag gag	152
	Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu	
	25 30 35	
15	ctc ggc gcc aac aag gcc acc ctg gtg tgc ctc atc agc gac ttc tac	200
	Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr	
	40 45 50	
20	ccc agt ggc gtg acg gtg gcc tgg aag gca gac ggc agc ccc gtc acc	248
	Pro Ser Gly Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Thr	
	55 60 65 70	
25	cag ggc gtg gag acc acc aag ccc tcc aag cag agc aac aac aag tac	296
	Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr	
	75 80 85	
30	gcg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac	344
	Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His	
	90 95 100	
35	agc agc ttc agc tgc ctg gtc aca cac gag ggg agc acc gtg gag aag	392
	Ser Ser Phe Ser Cys Leu Val Thr His Glu Gly Ser Thr Val Glu Lys	
	105 110 115	
40	aag gtg gcc ccc gca gag tgc tct tag gttcccgacg cccccgcca	439
	Lys Val Ala Pro Ala Glu Cys Ser	
	120 125	
45	cctaaggggg cccggagcct caggacctcc aggaggatct tgcctcctat ctggggtcatc	499
50	ccgcccttct cccacacccc aggcagcact caataaagtg ttctttgttc aa	551
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Ser Ile Pro Thr Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe
20 25 30

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

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

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

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

EP 2 305 300 B1

	ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg	144
	Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg	
	35 40 45	
5	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg	192
	Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu	
	50 55 60	
10	att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc	240
	Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe	
	65 70 75 80	
15	tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc	288
	Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala	
	85 90 95	
20	caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa agt agc	336
	Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser	
	100 105 110	
25	gct gat tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt	384
	Ala Asp Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly	
	115 120 125	
30	cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag	432
	Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu	
	130 135 140	
35	gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc	480
	Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe	
	145 150 155 160	
40	tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc	528
	Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile	
	165 170 175	
45	atc cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag	576
	Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys	
	180 185 190	
50	tac acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct	624
	Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser	
	195 200 205	
55	cac agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag	672
	His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu	
	210 215 220	
60	aag aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga	722
	Lys Lys Val Ala Pro Ala Glu Cys Ser	
	225 230	
65	tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgccct gaaaaccac	782
	cctggaccag ctcagaccag gcaggtcact catcctccct gtttctactt gtgctcaata	842
70	aagactttat catttatcac tg	864

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<212> PRT

<213> Canis familiaris

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15

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

20

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
50 55 60

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

25

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

30

Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
100 105 110

35

Ala Asp Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly
115 120 125

40

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

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

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

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

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

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His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
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EP 2 305 300 B1

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	1 5 10 15	
5	tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc	96
	Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr	
	20 25 30	
10	ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg	144
	Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg	
	35 40 45	
15	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg	192
	Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu	
	50 55 60	
20	att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc	240
	Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe	
	65 70 75 80	
25	tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc	288
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30	caa acc aac gat gag gct gac tat tac tgc cag gtg tgg gaa agt agc	336
	Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser	
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35	gct gat gct cac aac aac tct gga aga aaa att gga gca cct ggc agt	384
	Ala Asp Ala His Asn Asn Ser Gly Arg Lys Ile Gly Ala Pro Gly Ser	
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40	cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag	432
	Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu	
	130 135 140	
45	gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc	480
	Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe	
	145 150 155 160	
50	tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc	528
	Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile	
	165 170 175	
55	atc cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag	576

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

5 tac acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct 624
Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser
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10 cac agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag 672
His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu
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15 aag aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga 722
Lys Lys Val Ala Pro Ala Glu Cys Ser
225 230

20 tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgccct gaaaacccac 782
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35 40 45

45 Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
50 55 60

50 Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
65 70 75 80

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85 90 95

60 Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Glu Ser Ser
100 105 110

65 Ala Asp Ala His Asn Asn Ser Gly Arg Lys Ile Gly Ala Pro Gly Ser
115 120 125

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

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	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile	
				165					170						175		
10	cag	ggc	gtg	gaa	acc	acc	aag	ccc	tcc	aag	cag	agc	aac	aac	aag	tac	576
	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	
				180				185						190			
15	acg	gcc	agc	agc	tac	ctg	agc	ctg	acg	cct	gac	aag	tgg	aaa	tct	cac	624
	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	
			195					200					205				
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	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val	Glu	Lys	
			210				215					220					
20	aag	gtg	gcc	cct	gca	gag	tgc	tct	tag	gtccctgaga	attcctgaga						719
	Lys	Val	Ala	Pro	Ala	Glu	Cys	Ser									
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	Ser	Gly	Thr	Asn	Ser	Gly	Ser	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Glu	Ala	
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			115					120					125			
10	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu
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20	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile
				165						170					175	
25	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr
				180					185					190		
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			195					200					205			
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10	ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg	144
	Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg	
	35 40 45	
15	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg	192
	Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu	
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	Met	Ala	Trp	Thr	Leu	Leu	Leu	Leu	Gly	Phe	Leu	Ala	His	Cys	Thr	Gly
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	Ser	Val	Ala	Ser	Tyr	Val	Leu	Thr	Gln	Ser	Pro	Ser	Val	Ser	Val	Thr
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	Leu	Gly	Gln	Thr	Ala	Ser	Ile	Thr	Cys	Arg	Gly	Asn	Ser	Ile	Gly	Arg
			35					40					45			
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	Lys	Asp	Val	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Leu	Leu
		50					55					60				
	Ile	Ile	Tyr	Asn	Asp	Asn	Ser	Gln	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe
20	65					70					75					80
	Ser	Gly	Thr	Asn	Ser	Gly	Ser	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Glu	Ala
				85						90					95	
25																
	Gln	Thr	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Glu	Met	His	Thr	Pro
				100					105					110		
30																
	Glu	Ser	Gln	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	Thr	Val	Leu
			115					120					125			
	Gly	Gln	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser
35		130					135					140				
	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp
40	145					150					155					160
	Phe	Tyr	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr
					165					170					175	
45																
	Ile	Ile	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn
				180					185					190		
50																
	Lys	Tyr	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys
			195					200					205			
	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val
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5	tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc	96
	Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr	
	20 25 30	
10	ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg	144
	Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg	
	35 40 45	
15	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg	192
	Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu	
	50 55 60	
20	att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc	240
	Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe	
	65 70 75 80	
25	tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc	288
	Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala	
	85 90 95	
30	caa acc aac gat gag gct gac tat tac tgc cag cat tac cac cat gac	336
	Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln His Tyr His His Asp	
	100 105 110	
35	tat tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag	384
	Tyr Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln	
	115 120 125	
40	ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag	432
	Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu	
	130 135 140	
45	ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac	480
	Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr	
	145 150 155 160	
50	ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc	528
	Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile	
	165 170 175	
55	cag ggc gtg gaa acc acc aag ccc tcc aag cag agc aac aac aag tac	576
	Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr	
	180 185 190	
60	acg gcc agc agc tac ctg agc ctg acg cct gac aag tgg aaa tct cac	624
	Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp Lys Trp Lys Ser His	
	195 200 205	

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	agc agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag	672
	Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys	
	210 215 220	
5	aag gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga	719
	Lys Val Ala Pro Ala Glu Cys Ser	
	225 230	
10	tggagccttc ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaaccac	779
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					20					25					30			
10	Leu	Gly	Gln	Thr	Ala	Ser	Ile	Thr	Cys	Arg	Gly	Asn	Ser	Ile	Gly	Arg		
			35					40					45					
15	Lys	Asp	Val	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Leu	Leu		
		50					55					60						
	Ile	Ile	Tyr	Asn	Asp	Asn	Ser	Gln	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe		
	65					70					75					80		
20		Ser	Gly	Thr	Asn	Ser	Gly	Ser	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Glu	Ala	
					85						90					95		
25	Gln	Thr	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	His	Tyr	His	His	Asp		
				100					105					110				
30	Tyr	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	Thr	Val	Leu	Gly	Gln		
			115					120					125					
35	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu		
		130					135					140						
40	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr		
	145					150					155					160		
45	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile		
					165					170					175			
50	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr		
				180					185					190				
55	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His		
			195					200					205					
	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val	Glu	Lys		
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	1 5 10 15	
20	tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc	96
	Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr	
	20 25 30	
25	ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg	144
	Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg	
	35 40 45	
30	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg	192
	Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu	
	50 55 60	
35	att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc	240
	Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe	
	65 70 75 80	
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	Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala	
	85 90 95	
45	caa acc aac gat gag gct gac tat tac tgc cag gtc cat ggg ggg gga	336
	Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val His Gly Gly Gly	
	100 105 110	
50	ggg tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag	384

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			115					120					125				
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	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	
		130					135					140					
10	ctc	ggc	gcc	aac	aag	gct	acc	ctg	gtg	tgc	ctc	atc	agc	gac	ttc	tac	480
	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	
	145					150					155				160		
15	ccc	agt	ggc	ctg	aaa	gtg	gct	tgg	aag	gca	gat	ggc	agc	acc	atc	atc	528
	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile	
					165					170					175		
20	cag	ggc	gtg	gaa	acc	acc	aag	ccc	tcc	aag	cag	agc	aac	aac	aag	tac	576
	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	
				180					185					190			
25	acg	gcc	agc	agc	tac	ctg	agc	ctg	acg	cct	gac	aag	tgg	aaa	tct	cac	624
	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	
			195					200					205				
30	agc	agc	ttc	agc	tgc	ctg	gtc	acg	cac	cag	ggg	agc	acc	gtg	gag	aag	672
	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val	Glu	Lys	
		210					215					220					
35	aag	gtg	gcc	cct	gca	gag	tgc	tct	tag	gtccctgaga	attcctgaga						719
	Lys	Val	Ala	Pro	Ala	Glu	Cys	Ser									
	225					230											
40	tgagagccttc	ctcaccacaga	caccccttcc	ccagttcacc	ttgtgcccct	gaaaacccac											779
	cctggaccag	ctcagaccag	gcaggtcact	catcctccct	gtttctactt	gtgctcaata											839
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	1				5					10					15		
60	Ser	Val	Ala	Ser	Tyr	Val	Leu	Thr	Gln	Ser	Pro	Ser	Val	Ser	Val	Thr	
				20					25					30			
65	Leu	Gly	Gln	Thr	Ala	Ser	Ile	Thr	Cys	Arg	Gly	Asn	Ser	Ile	Gly	Arg	
			35					40					45				
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		50					55					60					
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				85						90					95	
10	Gln	Thr	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	His	Gly	Gly	Gly
				100					105					110		
15	Gly	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	Thr	Val	Leu	Gly	Gln
			115					120					125			
20	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu
		130					135					140				
25	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr
	145				150					155						160
30	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile
					165				170						175	
35	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr
				180					185					190		
40	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His
			195					200					205			
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5	tcc gtg gcc tcc tat gtg ctg act cag tca ccc tca gtg tca gtg acc	96
	Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr	
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10	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu 50 55 60	192		
15	att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe 65 70 75 80	240		
20	tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala 85 90 95	288		
25	caa acc aac gat gag gct gac tat tac tgc cag aaa cat cgg ggt gca Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Lys His Arg Gly Ala 100 105 110	336		
30	ggg tgt tgg gta ttc ggt gaa ggg acc cag ctg acc gtc ctc ggt cag Gly Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln 115 120 125	384		
35	ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu 130 135 140	432		
40	ctc ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr 145 150 155 160	480		
45	ccc agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile 165 170 175	528		
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15	Lys	Asp	Val	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Leu	Leu	
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35	Gly	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	Thr	Val	Leu	Gly	Gln	
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45	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	
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50	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile	
				165						170					175		
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				180					185					190			
60	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	
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30	aaa gat gtt cat tgg tac cag cag aag ccg ggc caa gcc ccc ctg ctg Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu 50 55 60	192
35	att atc tat aat gat aac agc cag ccc tca ggg atc cct gag cga ttc Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe 65 70 75 80	240
40	tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala 85 90 95	288
45	caa acc aac gat gag gct gac tat tac tgc cag gtg tcc ctt ggg tct Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Ser Leu Gly Ser 100 105 110	336
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55	aag tcc tcc ccc ttg gtc aca ctc ttc ccg ccc tcc tct gag gag ctc Lys Ser Ser Pro Leu Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu 130 135 140	432
60	ggc gcc aac aag gct acc ctg gtg tgc ctc atc agc gac ttc tac ccc Gly Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro 145 150 155 160	480
65	agt ggc ctg aaa gtg gct tgg aag gca gat ggc agc acc atc atc cag Ser Gly Leu Lys Val Ala Trp Lys Ala Asp Gly Ser Thr Ile Ile Gln 165 170 175	528

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 180 185 190

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10 agc ttc agc tgc ctg gtc acg cac cag ggg agc acc gtg gag aag aag 672
 Ser Phe Ser Cys Leu Val Thr His Gln Gly Ser Thr Val Glu Lys Lys
 210 215 220

15 gtg gcc cct gca gag tgc tct tag gtccctgaga attcctgaga tggagccttc 726
 Val Ala Pro Ala Glu Cys Ser
 225 230

ctcacccaga cacccttcc ccagttcacc ttgtgcccct gaaaaccac cctggaccag 786
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 35 40 45

Lys Asp Val His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Leu Leu
 50 55 60

45 Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe
 65 70 75 80

50 Ser Gly Thr Asn Ser Gly Ser Thr Ala Thr Leu Thr Ile Ser Glu Ala
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55 Gln Thr Asn Asp Glu Ala Asp Tyr Tyr Cys Gln Val Ser Leu Gly Ser
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Cys Trp Val Phe Gly Glu Gly Thr Gln Leu Thr Val Leu Gly Gln Pro
 115 120 125

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	145					150					155					160	
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					165					170					175		
15	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Thr	
				180					185					190			
20	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	
			195				200						205				
25	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val	Glu	Lys	Lys	
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	Ser Val Ala Ser Tyr Val Leu Thr Gln Ser Pro Ser Val Ser Val Thr	
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10	ctg gga cag acg gcc agc atc acc tgt agg gga aac agc att gga agg	144
	Leu Gly Gln Thr Ala Ser Ile Thr Cys Arg Gly Asn Ser Ile Gly Arg	
	35 40 45	
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	Ile Ile Tyr Asn Asp Asn Ser Gln Pro Ser Gly Ile Pro Glu Arg Phe	
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25	tct ggg acc aac tca ggg agc acg gcc acc ctg acc atc agt gag gcc	288
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				85						90					95		
5	caa	acc	aac	gat	gag	gct	gac	tat	tac	tgc	cag	gta	ttg	atg	gga	ggg	336
	Gln	Thr	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	Leu	Met	Gly	Gly	
				100					105					110			
10	tgt	tgg	gta	ttc	ggt	gaa	ggg	acc	cag	ctg	acc	gtc	ctc	ggt	cag	ccc	384
	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	Thr	Val	Leu	Gly	Gln	Pro	
			115					120					125				
15	aag	tcc	tcc	ccc	ttg	gtc	aca	ctc	ttc	ccg	ccc	tcc	tct	gag	gag	ctc	432
	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	
			130				135					140					
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	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	
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25	agt	ggc	ctg	aaa	gtg	gct	tgg	aag	gca	gat	ggc	agc	acc	atc	atc	cag	528
	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	Gly	Ser	Thr	Ile	Ile	Gln	
				165					170						175		
30	ggc	gtg	gaa	acc	acc	aag	ccc	tcc	aag	cag	agc	aac	aac	aag	tac	acg	576
	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Thr	
				180					185					190			
35	gcc	agc	agc	tac	ctg	agc	ctg	acg	cct	gac	aag	tgg	aaa	tct	cac	agc	624
	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	
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40	agc	ttc	agc	tgc	ctg	gtc	acg	cac	cag	ggg	agc	acc	gtg	gag	aag	aag	672
	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val	Glu	Lys	Lys	
		210					215					220					
45	gtg	gcc	cct	gca	gag	tgc	tct	tag	gtccctgaga	attcctgaga	tggagccttc						726
	Val	Ala	Pro	Ala	Glu	Cys	Ser										
	225					230											
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		50					55					60					
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20	Gln	Thr	Asn	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Val	Leu	Met	Gly	Gly	
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25	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	Thr	Val	Leu	Gly	Gln	Pro	
			115					120					125				
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		130					135					140					
35	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	
	145					150					155					160	
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				180					185					190			
50	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	
			195					200					205				
55	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	Ser	Thr	Val	Glu	Lys	Lys	
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	Leu Phe Met Ser Val Ala Leu Gly Gln Met Ala Arg Ile Thr Cys Gly	
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10	aga gac aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca	144
	Arg Asp Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro	
	35 40 45	
15	agc cag gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca	192
	Ser Gln Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser	
	50 55 60	
	gga ttc tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc	240
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	Leu Thr Ile Ser Gly Pro Pro Ala Arg Thr Gln Val Arg Tyr Ala Gln	
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25	ccc ggg gct cca ggg gca ggg act tgt tgg gta ttc ggt gaa ggg acc	336
	Pro Gly Ala Pro Gly Ala Gly Thr Cys Trp Val Phe Gly Glu Gly Thr	
	100 105 110	
30	cag ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc	384
	Gln Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu	
	115 120 125	
	ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg	432
	Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val	
	130 135 140	
35	tgc ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag	480
	Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys	
	145 150 155 160	
40	gca gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc	528
	Ala Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser	
	165 170 175	
45	aag cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg	576
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	180 185 190	
	cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac	624
	Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His	
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	Gln Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
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55	gtccctgaga attcctgaga tggagccttc ctcaccaga cacccttcc ccagttcacc	732
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5		Leu	Phe	Met	Ser	Val	Ala	Leu	Gly	Gln	Met	Ala	Arg	Ile	Thr	Cys	Gly	
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10		Arg	Asp	Asn	Ser	Gly	Arg	Lys	Ser	Ala	His	Trp	Tyr	Gln	Gln	Lys	Pro	
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25		Pro	Gly	Ala	Pro	Gly	Ala	Gly	Thr	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	
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30		Gln	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	
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		Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	
			130					135					140					
35		Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	
		145					150					155					160	
40		Ala	Asp	Gly	Ser	Thr	Ile	Ile	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	
						165					170					175		
45		Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	
					180					185					190			
50		Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	
				195					200					205				
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15	aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln 20 25 30	96
20	gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe 35 40 45	144
25	tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr 50 55 60	192
30	att aaa gaa atg gac gca ttc ctg gaa acc tcc ttc tat tgc tgg atg Ile Lys Glu Met Asp Ala Phe Leu Glu Thr Ser Phe Tyr Cys Trp Met 65 70 75 80	240
35	tgg cag cct gaa tca cag tgt tgg gta ttc ggt gaa ggg acc cag ctg Trp Gln Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr Gln Leu 85 90 95	288
40	acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc ccg Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro 100 105 110	336
45	ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu 115 120 125	384
50	atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp 130 135 140	432
55	ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag cag Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln 145 150 155 160	480
	agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct gac Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp 165 170 175	528

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	aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag ggg	576
	Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly	
	180 185 190	
5	agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag	618
	Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	195 200 205	
10	gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc	678
	ttgtgcccct gaaaaccac cctggaccag ctcagaccag gcaggtcact catcctccct	738
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5	Asn	Ser	Gly	Arg	Lys	Ser	Ala	His	Trp	Tyr	Gln	Gln	Lys	Pro	Ser	Gln	
				20					25					30			
10	Ala	Pro	Val	Met	Leu	Ile	Asp	Asp	Asp	Cys	Phe	Gln	Pro	Ser	Gly	Phe	
			35				40						45				
15	Ser	Glu	Gln	Phe	Ser	Gly	Thr	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	
	50						55					60					
	Ile	Lys	Glu	Met	Asp	Ala	Phe	Leu	Glu	Thr	Ser	Phe	Tyr	Cys	Trp	Met	
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20	Trp	Gln	Pro	Glu	Ser	Gln	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	
					85					90					95		
25	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	
				100					105					110			
30	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	
			115					120					125				
	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	
	130						135					140					
35	Gly	Ser	Thr	Ile	Ile	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	
	145					150					155					160	
40																	
	Ser	Asn	Asn	Lys	Tyr	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	
					165					170					175		
45	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	
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10	aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag	96
	Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln	
	20 25 30	
15	gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc	144
	Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe	
	35 40 45	
20	tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc	192
	Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr	
	50 55 60	
25	att agt gtg tca aac att gac gac acg ctt tac ata tat aga acg gaa	240
	Ile Ser Val Ser Asn Ile Asp Asp Thr Leu Tyr Ile Tyr Arg Thr Glu	
	65 70 75 80	
	gtg agc aac att cct gaa tca cag tgt tgg gta ttc ggt gaa ggg acc	288
	Val Ser Asn Ile Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr	
	85 90 95	
30	cag ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc	336
	Gln Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu	
	100 105 110	
35	ttc ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg	384
	Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val	
	115 120 125	
40	tgc ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag	432
	Cys Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys	
	130 135 140	
	gca gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc	480

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	145 150 155 160	
5	aag cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg	528
	Lys Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr	
	165 170 175	
10	cct gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac	576
	Pro Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His	
	180 185 190	
15	cag ggg agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag	624
	Gln Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	195 200 205	
20	gtccctgaga attcctgaga tggagccttc ctcaccagaga cacccttcc ccagttcacc	684
	ttgtgccctt gaaaaccac cctggaccag ctcagaccag gcaggtcact catcctccct	744
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40	Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe	
	35 40 45	
45	Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr	
	50 55 60	
50	Ile Ser Val Ser Asn Ile Asp Asp Thr Leu Tyr Ile Tyr Arg Thr Glu	
	65 70 75 80	
55	Val Ser Asn Ile Pro Glu Ser Gln Cys Trp Val Phe Gly Glu Gly Thr	
	85 90 95	
60	Gln Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu	
	100 105 110	
65	Phe Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val	
	115 120 125	

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	145					150					155					160
10	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr
					165					170					175	
15	Pro	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His
				180					185					190		
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	Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln	
	20 25 30	
10	gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc	144
	Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe	
	35 40 45	
15	tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc	192
	Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr	
	50 55 60	
20	att agt gga cac cgt gca gaa cca gag gca gaa cat ttc tct ctg tgg	240
	Ile Ser Gly His Arg Ala Glu Pro Glu Ala Glu His Phe Ser Leu Trp	
	65 70 75 80	
25	cca tgc aag tca gat cct ggt tgt tgg gta ttc ggt gaa ggg acc cag	288
	Pro Cys Lys Ser Asp Pro Gly Cys Trp Val Phe Gly Glu Gly Thr Gln	
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30	ctg acc gtc ctc ggt cag ccc aag tcc tcc ccc ttg gtc aca ctc ttc	336
	Leu Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe	
	100 105 110	
35	ccg ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc	384
	Pro Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys	
	115 120 125	
40	ctc atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca	432
	Leu Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala	
	130 135 140	
45	gat ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag	480
	Asp Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys	
	145 150 155 160	
50	cag agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct	528
	Gln Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro	
	165 170 175	
55	gac aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag	576
	Asp Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln	
	180 185 190	
60	ggg agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag	621
	Gly Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	195 200 205	
65	gtccctgaga attcctgaga tggagccttc ctacaccaga cacccttcc ccagttcacc	681
70	ttgtgccctt gaaaaccac cctggaccag ctgagaccag gcaggtcact catcctccct	741
75	gtttctactt gtgctcaata aagactttat catttatcac tg	783

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 <213> Canis familiaris

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20	Ser	Glu	Gln	Phe	Ser	Gly	Thr	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr
		50					55					60				
	Ile	Ser	Gly	His	Arg	Ala	Glu	Pro	Glu	Ala	Glu	His	Phe	Ser	Leu	Trp
25	65					70					75					80
	Pro	Cys	Lys	Ser	Asp	Pro	Gly	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln
					85					90					95	
30	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe
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	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys
			115					120					125			
40	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala
		130					135					140				
	Asp	Gly	Ser	Thr	Ile	Ile	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys
45	145					150					155					160
	Gln	Ser	Asn	Asn	Lys	Tyr	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro
50					165					170					175	
	Asp	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln
				180					185					190		
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20	aac tct gga aga aaa agt gct cac tgg tac cag cag aag cca agc cag	96
	Asn Ser Gly Arg Lys Ser Ala His Trp Tyr Gln Gln Lys Pro Ser Gln	
	20 25 30	
25	gct ccc gtg atg ctt atc gat gat gat tgc ttc cag ccc tca gga ttc	144
	Ala Pro Val Met Leu Ile Asp Asp Asp Cys Phe Gln Pro Ser Gly Phe	
	35 40 45	
30	tct gag caa ttc tca ggc act aac tcg ggg aac aca gcc acc ctg acc	192
	Ser Glu Gln Phe Ser Gly Thr Asn Ser Gly Asn Thr Ala Thr Leu Thr	
	50 55 60	
35	att agt cag atc cca ccc tac tct gaa gtg act cgc ttc act cgg gcc	240
	Ile Ser Gln Ile Pro Pro Tyr Ser Glu Val Thr Arg Phe Thr Arg Ala	
	65 70 75 80	
40	tgg gca gac act agc tgt tgt tgg gta ttc ggt gaa ggg acc cag ctg	288
	Trp Ala Asp Thr Ser Cys Cys Trp Val Phe Gly Glu Gly Thr Gln Leu	
	85 90 95	

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	Thr Val Leu Gly Gln Pro Lys Ser Ser Pro Leu Val Thr Leu Phe Pro	
	100 105 110	
5	ccc tcc tct gag gag ctc ggc gcc aac aag gct acc ctg gtg tgc ctc	384
	Pro Ser Ser Glu Glu Leu Gly Ala Asn Lys Ala Thr Leu Val Cys Leu	
	115 120 125	
10	atc agc gac ttc tac ccc agt ggc ctg aaa gtg gct tgg aag gca gat	432
	Ile Ser Asp Phe Tyr Pro Ser Gly Leu Lys Val Ala Trp Lys Ala Asp	
	130 135 140	
15	ggc agc acc atc atc cag ggc gtg gaa acc acc aag ccc tcc aag cag	480
	Gly Ser Thr Ile Ile Gln Gly Val Glu Thr Thr Lys Pro Ser Lys Gln	
	145 150 155 160	
20	agc aac aac aag tac acg gcc agc agc tac ctg agc ctg acg cct gac	528
	Ser Asn Asn Lys Tyr Thr Ala Ser Ser Tyr Leu Ser Leu Thr Pro Asp	
	165 170 175	
25	aag tgg aaa tct cac agc agc ttc agc tgc ctg gtc acg cac cag ggg	576
	Lys Trp Lys Ser His Ser Ser Phe Ser Cys Leu Val Thr His Gln Gly	
	180 185 190	
30	agc acc gtg gag aag aag gtg gcc cct gca gag tgc tct tag	618
	Ser Thr Val Glu Lys Lys Val Ala Pro Ala Glu Cys Ser	
	195 200 205	
35	gtccctgaga attcctgaga tggagccttc ctcacccaga cacccttcc ccagttcacc	678
40	ttgtgcccct gaaaaccac cctggaccag ctcagaccag gcaggtcact catcctccct	738
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				20					25					30			
10	Ala	Pro	Val	Met	Leu	Ile	Asp	Asp	Asp	Cys	Phe	Gln	Pro	Ser	Gly	Phe	
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15	Ser	Glu	Gln	Phe	Ser	Gly	Thr	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	
	50					55					60						
20	Ile	Ser	Gln	Ile	Pro	Pro	Tyr	Ser	Glu	Val	Thr	Arg	Phe	Thr	Arg	Ala	
	65				70					75						80	
25	Trp	Ala	Asp	Thr	Ser	Cys	Cys	Trp	Val	Phe	Gly	Glu	Gly	Thr	Gln	Leu	
				85					90						95		
30	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ser	Ser	Pro	Leu	Val	Thr	Leu	Phe	Pro	
			100					105						110			
35	Pro	Ser	Ser	Glu	Glu	Leu	Gly	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	
			115				120						125				
40	Ile	Ser	Asp	Phe	Tyr	Pro	Ser	Gly	Leu	Lys	Val	Ala	Trp	Lys	Ala	Asp	
	130					135					140						
45	Gly	Ser	Thr	Ile	Ile	Gln	Gly	Val	Glu	Thr	Thr	Lys	Pro	Ser	Lys	Gln	
	145				150					155						160	
50	Ser	Asn	Asn	Lys	Tyr	Thr	Ala	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Asp	
				165					170						175		
55	Lys	Trp	Lys	Ser	His	Ser	Ser	Phe	Ser	Cys	Leu	Val	Thr	His	Gln	Gly	
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10	ctg gct ctc tgc aca ggt tct gtg gcc tcc tat gtg ctg aca cag ctg	101
	Leu Ala Leu Cys Thr Gly Ser Val Ala Ser Tyr Val Leu Thr Gln Leu	
	15 20 25	
15	cca tcc aaa aat gtg acc ctg aag cag ccg gcc cac atc acc tgt ggg	149
	Pro Ser Lys Asn Val Thr Leu Lys Gln Pro Ala His Ile Thr Cys Gly	
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	60 65 70	
5	ggg atc cct gag cga ttc tcc ggc gcc aac tcg ggg aac acg gcc acc	293
	Gly Ile Pro Glu Arg Phe Ser Gly Ala Asn Ser Gly Asn Thr Ala Thr	
	75 80 85 90	
10	ctg acc atc agc ggg gcc ctg gcc gag gac gag gct gac tat tac tgc	341
	Leu Thr Ile Ser Gly Ala Leu Ala Glu Asp Glu Ala Asp Tyr Tyr Cys	
	95 100 105	
15	cag gtg tgg gac agc agt gct ctt gtg ttc ggc gga ggc acc cat ctg	389
	Gln Val Trp Asp Ser Ser Ala Leu Val Phe Gly Gly Gly Thr His Leu	
	110 115 120	
20	acc gtc ctc ggt cag ccc aag gcc tcc ccc tcg gtc aca ctc ttc ccg	437
	Thr Val Leu Gly Gln Pro Lys Ala Ser Pro Ser Val Thr Leu Phe Pro	
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Claims

- 45 1. An antibody for use in a method of therapy and/or prophylaxis of cancer, said antibody having immunoreactivity to a CD179b protein having the amino acid sequence shown in SEQ ID NO:3, wherein the antibody is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells and complement-dependent cytotoxicity (CDC) against CD179-expressing cells.
- 50 2. The antibody for use according to claim 1, wherein said cancer is leukemia or lymphoma.
3. The antibody for use according to claim 1 or 2, wherein said antibody is a monoclonal antibody or a polyclonal antibody.
4. The antibody for use according to any one of claims 1 to 3, wherein said antibody is a human antibody, humanized antibody, chimeric antibody, single-chain antibody or bispecific antibody.
- 55 5. An antibody comprising a heavy chain variable region having the amino acid sequences shown in SEQ ID NOs:103, 104 and 102 for CDR1, CDR2 and CDR3 respectively and a light chain variable region having the amino acid sequences shown in SEQ ID NOs: 106, 107 and 108 for CDR1, CDR2 and CDR3 respectively, said antibody having

immunoreactivity to a CD179b protein, wherein the antibody is capable of mediating antibody-dependent cell-mediated cytotoxicity (ADCC) by effector cells and complement-dependent cytotoxicity (CDC) against CD179-expressing cells.

- 5 6. The antibody of claim 5, which comprises a heavy chain variable region having the amino acid sequence shown in SEQ ID NO:105 and a light chain variable region having the amino acid sequence shown in SEQ ID NO:109.
7. The antibody according to claim 5 or 6, which is a humanized antibody, chimeric antibody, single-chain antibody or bispecific antibody.
- 10 8. The antibody of any one of claims 5 to 7, for use in a method of medical treatment.
9. The antibody for use according to any one of claims 1 to 4, wherein said antibody is the antibody according to any one of claims 5 to 7.
- 15 10. A pharmaceutical composition comprising as an effective component an antibody according to any one of claims 5 to 7.
11. A DNA encoding the antibody of any one of claims 5 to 7.

Patentansprüche

- 25 1. Antikörper zur Verwendung in einem Therapie- und/oder Prophylaxeverfahren gegen Krebs, wobei der Antikörper eine Immunreaktivität auf ein CD179b-Protein aufweist, das die in SEQ-ID Nr. 3 gezeigte Aminosäuresequenz aufweist, worin der Antikörper fähig ist, eine antikörperabhängige zellvermittelte Zytotoxizität (ADCC) durch Effektorzellen und eine komplementabhängige Zytotoxizität (CDC) gegen CD179-exprimierende Zellen zu vermitteln.
- 30 2. Antikörper zur Verwendung nach Anspruch 1, worin der Krebs Leukämie oder ein Lymphom ist.
3. Antikörper zur Verwendung nach Anspruch 1 oder 2, worin der Antikörper ein monoklonaler Antikörper oder ein polyklonaler Antikörper ist.
- 35 4. Antikörper zur Verwendung nach einem der Ansprüche 1 bis 3, worin der Antikörper ein menschlicher Antikörper, humanisierter Antikörper, chimärer Antikörper, einkettiger Antikörper oder bispezifischer Antikörper ist.
- 40 5. Antikörper, umfassend eine variable Schwarkettenregion, die die in SEQ-ID Nr. 103, 104 und 102 gezeigten Aminosäuresequenzen für CDR1, CDR2 bzw. CDR3 aufweist, und eine variable Leichtkettenregion, die die in SEQ-ID Nr. 106, 107 und 108 gezeigten Aminosäuresequenzen für CDR1, CDR2 bzw. CDR3 aufweist, wobei der Antikörper eine Immunreaktivität auf ein CD179b-Protein aufweist, worin der Antikörper fähig ist, eine antikörperabhängige zellvermittelte Zytotoxizität (ADCC) durch Effektorzellen und eine komplementabhängige Zytotoxizität (CDC) gegen CD179-exprimierende Zellen zu vermitteln.
- 45 6. Antikörper nach Anspruch 5, der eine variable Schwarkettenregion, die die in SEQ-ID Nr. 105 gezeigte Aminosäuresequenz aufweist, und eine variable Leichtkettenregion, die die in SEQ-ID Nr. 109 gezeigte Aminosäuresequenz aufweist, umfasst.
7. Antikörper nach Anspruch 5 oder 6, der ein humanisierter Antikörper, chimärer Antikörper, einkettiger Antikörper oder bispezifischer Antikörper ist.
- 50 8. Antikörper nach einem der Ansprüche 5 bis 7 zur Verwendung in einem medizinischen Behandlungsverfahren.
9. Antikörper zur Verwendung nach einem der Ansprüche 1 bis 4, worin der Antikörper ein Antikörper nach einem der Ansprüche 5 bis 7 ist.
- 55 10. Pharmazeutische Zusammensetzung, die als einen Wirkbestandteil einen Antikörper nach einem der Ansprüche 5 bis 7 umfasst.

11. DNA, die für einen Antikörper nach einem der Ansprüche 5 bis 7 kodiert.

Revendications

1. Anticorps destiné à être utilisé dans un procédé de thérapie et/ou de prophylaxie du cancer, ledit anticorps présentant une réactivité immunologique avec une protéine CD179b possédant la séquence d'acides aminés montrée dans SEQ ID NO: 3, où l'anticorps est capable de médier une cytotoxicité à médiation cellulaire dépendante des anticorps (ADCC) par des cellules effectrices et une cytotoxicité dépendante du complément (CDC) contre des cellules exprimant CD179.
2. Anticorps destiné à être utilisé selon la revendication 1, où ledit cancer est une leucémie ou un lymphome.
3. Anticorps destiné à être utilisé selon la revendication 1 ou 2, où ledit anticorps est un anticorps monoclonal ou un anticorps polyclonal.
4. Anticorps destiné à être utilisé selon l'une quelconque des revendications 1 à 3, où ledit anticorps est un anticorps humain, un anticorps humanisé, un anticorps chimérique, un anticorps simple chaîne ou un anticorps bispécifique.
5. Anticorps comprenant une région variable de chaîne lourde possédant les séquences d'acides aminés montrées dans SEQ ID NO: 103, 104 et 102 pour la CDR1, CDR2 et CDR3 respectivement et une région variable de chaîne légère possédant les séquences d'acides aminés montrées dans SEQ ID NO: 106, 107 et 108 pour la CDR1, CDR2 et CDR3 respectivement, ledit anticorps présentant une réactivité immunologique avec une protéine CD179b, où l'anticorps est capable de médier une cytotoxicité à médiation cellulaire dépendante des anticorps (ADCC) par des cellules effectrices et une cytotoxicité dépendante du complément (CDC) contre des cellules exprimant CD179.
6. Anticorps selon la revendication 5, qui comprend une région variable de chaîne lourde possédant la séquence d'acides aminés montrée dans SEQ ID NO: 105 et une région variable de chaîne légère possédant la séquence d'acides aminés montrée dans SEQ ID NO: 109.
7. Anticorps selon la revendication 5 ou 6, qui est un anticorps humanisé, un anticorps chimérique, un anticorps simple chaîne ou un anticorps bispécifique.
8. Anticorps selon l'une quelconque des revendications 5 à 7, destiné à être utilisé dans un procédé de traitement médical.
9. Anticorps destiné à être utilisé selon l'une quelconque des revendications 1 à 4, où ledit anticorps est l'anticorps selon l'une quelconque des revendications 5 à 7.
10. Composition pharmaceutique comprenant, en tant que composant efficace, un anticorps selon l'une quelconque des revendications 5 à 7.
11. ADN codant pour l'anticorps selon l'une quelconque des revendications 5 à 7.

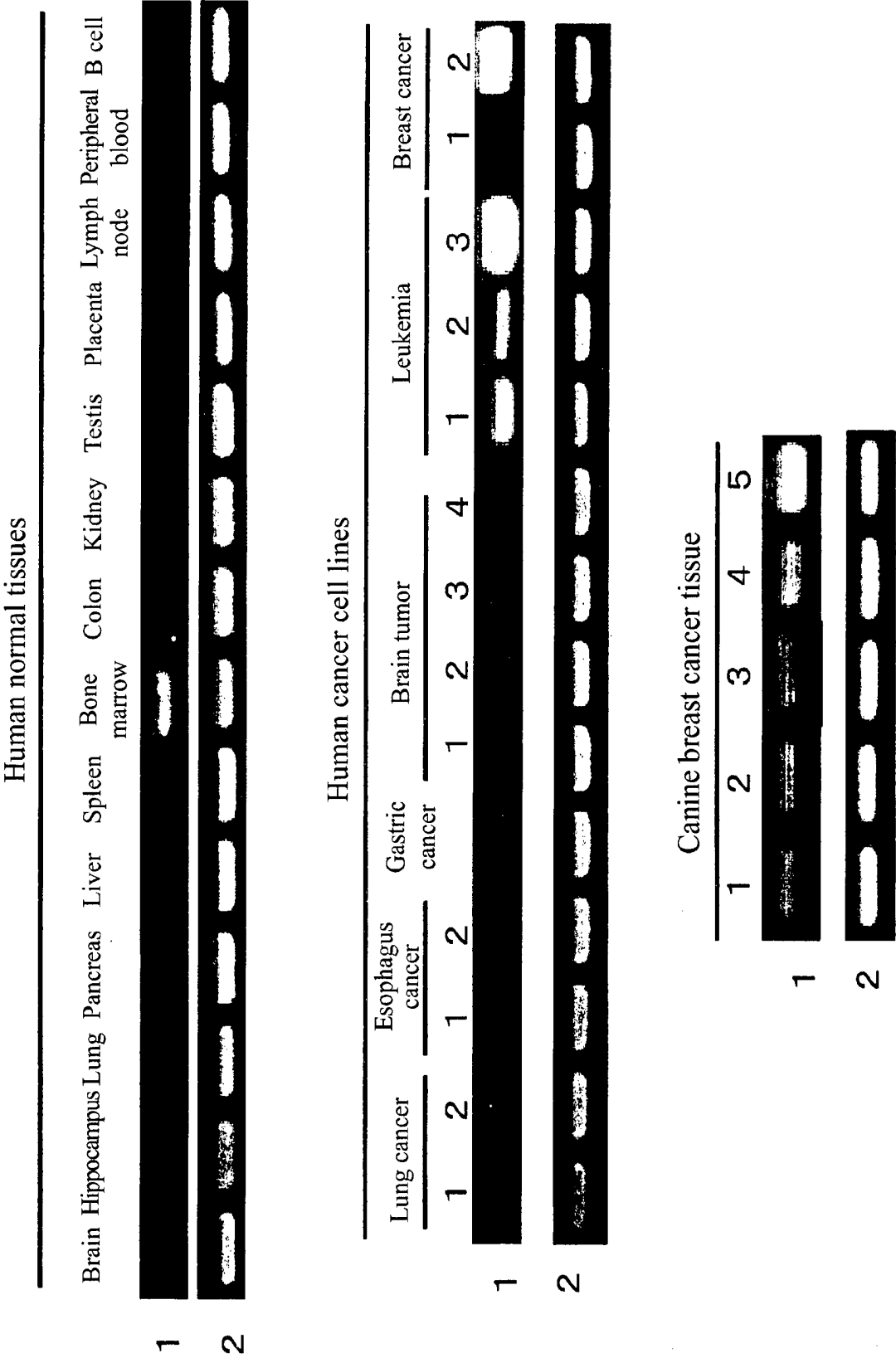
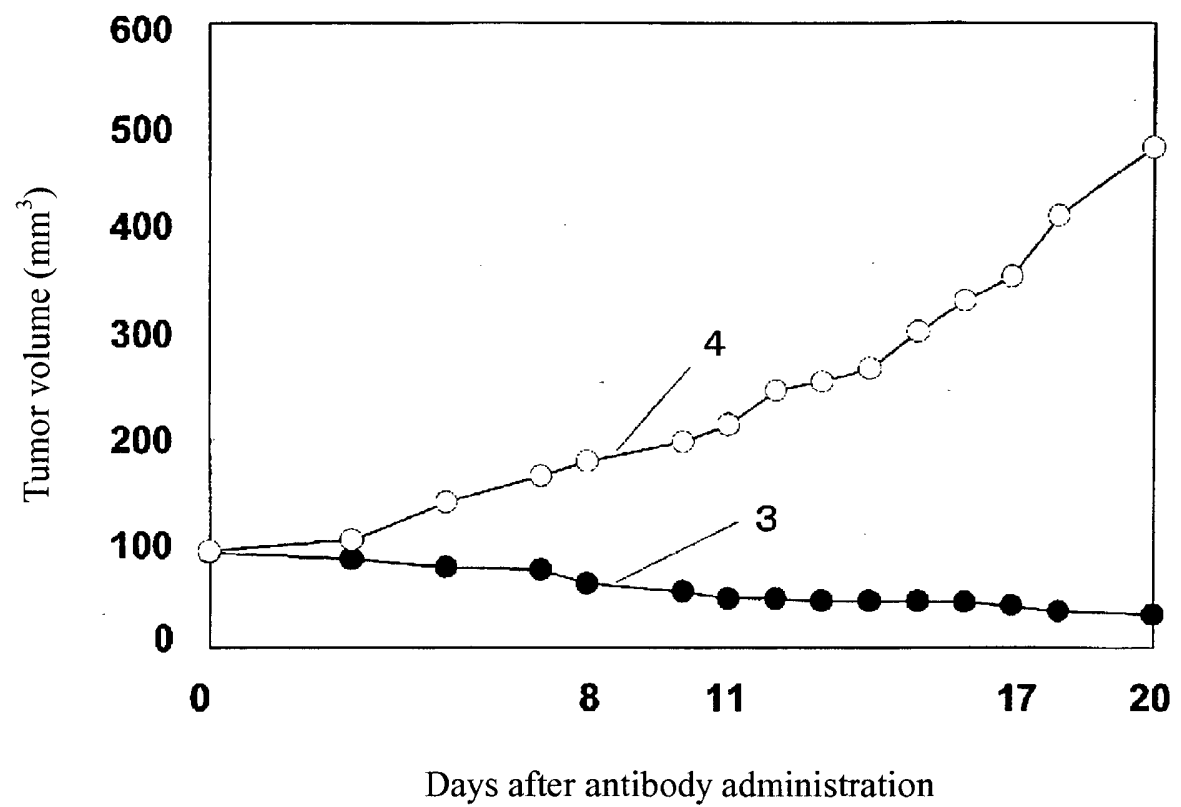


Fig.1

**Fig.2**

REFERENCES CITED IN THE DESCRIPTION

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GYÓGYÁSZATI KÉSZÍTMÉNY RÁK KEZELÉSÉRE ÉS MEGELŐZÉSÉRE

Szabadalmi igénypontok

1. Antitest rákterápiás és/vagy rákmegelőzési eljárásban történő alkalmazásra, amely antitest immunreaktivitást mutat egy CD179b fehérjével szemben, amely rendelkezik a SEQ ID NO:3-ban (azaz 3-as azonosítási számú szekvenciában) bemutatott aminosav-szekvenciával, ahol az antitest képes effektorsejtek általi antitest-dependens sejt-mediált citotoxicitás (ADCC) és CD179-expresszáló sejtekkel szembeni komplementfüggő citotoxicitás (CDC) mediálására.
2. Az antitest alkalmazásra az 1. igénypont szerint, ahol a rák leukémia vagy limfóma.
3. Az antitest alkalmazásra az 1. vagy 2. igénypont szerint, ahol az antitest monoklonális antitest vagy poliklonális antitest.
4. Az antitest alkalmazásra az 1-3. igénypontok bármelyike szerint, ahol az antitest humán antitest, humanizált antitest, kiméra antitest, egyláncú antitest vagy bispecifikus antitest.
5. Antitest, amely tartalmaz olyan nehézlánc variábilis régiót, amely rendelkezik a SEQ ID NO:103-ban bemutatott CDR1 aminosav-szekvenciával, a SEQ ID NO:104-ben bemutatott CDR2 aminosav-szekvenciával, és a SEQ ID NO:102-ben bemutatott CDR3 aminosav-szekvenciával, és tartalmaz olyan könnyűlánc variábilis régiót, amely rendelkezik a SEQ ID NO:106-ban bemutatott CDR1 aminosav-szekvenciával, a SEQ ID NO:107-ben bemutatott CDR2 aminosav-szekvenciával, és a SEQ ID NO:108-ban bemutatott CDR3 aminosav-szekvenciával, az antitest immunreaktivitást mutat egy CD179b fehérjével szemben, ahol az antitest képes effektorsejtek általi antitest-dependens sejt-

mediált citotoxicitás (ADCC) és CD179-expresszáló sejtekkel szembeni komplementfüggő citotoxicitás (CDC) mediálására.

6. Az 5. igénypont szerinti antitest, amely tartalmaz olyan nehézlánc variábilis régiót, amely rendelkezik a SEQ ID NO:105-ben bemutatott aminosav-szekvenciával, és olyan könnyűlánc variábilis régiót, amely rendelkezik a SEQ ID NO:109-ben bemutatott aminosav-szekvenciával.
7. Az 5. vagy 6. igénypont szerinti antitest, amely humanizált antitest, kiméra antitest, egyláncú antitest vagy bispecifikus antitest.
8. Az 5-7. igénypontok bármelyike szerinti antitest gyógyászati kezelési eljárásban történő alkalmazásra.
9. Az antitest alkalmazásra az 1-4. igénypontok bármelyike szerint, ahol az antitest az 5-7. igénypontok bármelyike szerinti antitest.
10. Gyógyászati készítmény, amely határos összetevőként tartalmaz az 5-7. igénypontok bármelyike szerinti antitestet.
11. DNS, amely kódolja az 5-7. igénypontok bármelyike szerinti antitestet.