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(72) Feltaláló(k): OKANO, Fumiyoshi, Kamakura-shi Kanagawa 248-8555 (JP) SAITO, Takanori, Kamakura-shi Kanagawa 248-8555 (JP)	(74) Képviselő: Frankné Dr. Machytka Daisy, Gödölle, Kékes, Mészáros & Szabó Szabadalmi és Védjegy Iroda, Budapest

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(54) **MEDICINAL COMPOSITION FOR TREATING AND/OR PREVENTING CANCER**

MEDIZINISCHE ZUSAMMENSETZUNG ZUR BEHANDLUNG ODER PRÄVENTION VON KREBS
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(74) Representative: **Denison, Christopher Marcus
Mewburn Ellis LLP
33 Gutter Lane
London
EC2V 8AS (GB)**

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WO-A2-2005/100998**

(73) Proprietor: **Toray Industries, Inc.
Tokyo 103-8666 (JP)**

- **KOLOBOVA, E. ET AL.: 'Microtubule-dependent association of AKAP350A and CCAR1 with RNA stress granules' EXPERIMENTAL CELL RESEARCH vol. 315, 2009, pages 542 - 555, XP025875180**

(72) Inventors:
• **OKANO, Fumiyoshi
Kamakura-shi
Kanagawa 248-8555 (JP)**
• **SAITO, Takanori
Kamakura-shi
Kanagawa 248-8555 (JP)**

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Description

Technical Field

5 **[0001]** The present invention relates to a novel pharmaceutical use of an antibody against CAPRIN-1 or a fragment thereof, as an agent, for treating and/or preventing a cancer.

Background Art

10 **[0002]** Cancer is the leading cause of death. Currently conducted therapy comprises mainly surgical therapy in combination with radiation therapy and chemotherapy. In spite of the development of new operative procedures and the discovery of new anticancer agents in recent years, cancer treatment results have not been much improved recently, excluding that for some types of cancer. Recent advances in molecular biology or cancer immunology lead to identification of antibodies specifically reacting with cancer, cancer antigens to be recognized by cytotoxic T cells, genes encoding cancer antigens, and the like. Demands on specific cancer therapies targeting cancer antigens are increasing (Non-patent Literature 1).

15 **[0003]** In cancer therapy, it is desirable that peptides, polypeptides, or proteins recognized as antigens be almost absent in normal cells, but they be present specifically in cancer cells, in order to alleviate side effects. In 1991, Boon et al., (Ludwig Institute for Cancer Research, Belgium) isolated a human melanoma antigen MAGE1 recognized by CD8-positive T cells by the cDNA expression cloning method using autologous cancer cell lines and cancer-reactive T cells (Non-patent Literature 2). Thereafter, the SEREX (serological identification of antigens by recombinant expression cloning) method that comprises identifying tumor antigens recognized by antibodies that are produced *in vivo* in response to autologous cancer of a cancer patient by gene expression cloning techniques was reported (Non-patent Literature 3 and Patent Literature 1). With the use of this method, some cancer antigens, which are almost never expressed in normal cells but are specifically expressed in cancer cells, were isolated (Non-patent Literatures 4-9). Furthermore, clinical trials were conducted with cell therapies targeting some cancer antigens using immunocytes specifically reactive with cancer antigens, or cancer-specific immunotherapies using vaccines or the like containing cancer antigens.

20 **[0004]** Meanwhile, in recent years, various antibody medicines which target antigenic proteins on cancer cells for cancer treatment have appeared throughout the world. Antibody medicines exhibit some pharmacological effects as cancer specific therapeutic agents and are thus attracting attention. However, most antigen proteins to be targeted are also expressed in normal cells, so that not only cancer cells, but also normal cells expressing antigens are also damaged as a result of antibody administration. The resulting side effects cause for concern. Therefore, it is expected that identification of cancer antigens that are specifically expressed on the surface of a cancer cell and use of antibodies targeting the cancer antigens as pharmaceuticals will realize treatment with antibody medicines with lower side effects.

25 **[0005]** Cytoplasmic- and proliferation-associated protein 1 (CAPRIN-1) is expressed when normal cells at the resting phase are activated or undergo cell division, and it is an intracellular protein known to form intracellular stress granules with RNA within cells, so as to be involved in mRNA transport and translational regulation. Meanwhile, many other names that represent CAPRIN-1 exist, such as GPI-anchored membrane protein 1 or membrane component surface marker 1 protein (M11S1), as if such proteins had been known to be cell membrane proteins. These names originated from a report that the gene sequence of CAPRIN-1 is a membrane protein having a GPI-binding region and expressed in colorectal cancer cells (Non-patent Literature 10). However, the gene sequence of CAPRIN-1 provided in this report was later revealed to be wrong. The following has recently been reported; i.e., deletion of a single nucleotide in the gene sequence of CAPRIN-1 registered at GenBank or the like causes a frame shift, so that 80 amino acids are lost from the C-terminus, resulting in generation of an artifact (74 amino acids) which corresponds to the GPI-binding portion in the previous report, and additionally, another error is also present 5' of the gene sequence, so that 53 amino acids were lost from the N-terminus (Non-patent Literature 11). It has been also recently reported that the protein encoded by the gene sequence of CAPRIN-1 registered at GenBank or the like is not a cell membrane protein (Non-patent Literature 11).

30 **[0006]** In addition, on the basis of the report of Non-patent Literature 10 that CAPRIN-1 is a cell membrane protein, Patent Literatures 2 and 3 describe that CAPRIN-1 (as a cell membrane protein) under the name of M11S1 can be used as a target of an antibody medicine in cancer therapy, although working examples do not describe treatment using an antibody against the protein. However, as reported in Non-patent Literature 11, it has been commonly believed from the time of the filing of Patent Literature 2 to date that CAPRIN-1 is not expressed on the surface of a cell. The contents of Patent Literatures 2 and 3 based only on incorrect information that CAPRIN-1 is a cell membrane protein should not clearly be understood as common general knowledge for persons skilled in the art.

35 **[0007]** Patent Literature 4 describes an antibody to the M11S1 protein and Non-patent Literature 12 describes a rabbit anti-CAPRIN-1 antibody that is used to detect CAPRIN-1.

Prior Art Literature

Patent Literature

5 [0008]

Patent Literature 1: U.S. Patent No. 5698396

Patent Literature 2: US2008/0075722

Patent Literature 3: WO2005/100998

10 Patent Literature 4: WO02/078524

Non-patent Literature

15 [0009]

Non-patent Literature 1: Tsuyoshi Akiyoshi, "Gan To Kagaku-Ryoho (Cancer and Chemotherapy)," 1997, Vol. 24, p551-519 (Cancer and Chemotherapy Publishers, Inc., Japan)

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

Non-patent Literature 3: Proc. Natl. Acad. Sci. U.S.A., 92: 11810-11813 (1995)

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

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

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

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

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

25 Non-patent Literature 9: Hum. Mol. Genet6: 33-39, 1997

Non-patent Literature 10: J. Biol. Chem., 270: 20717-20723, 1995

Non-patent Literature 11: J. Immunol., 172: 2389-2400, 2004

Non-patent Literature 12: Kolobova E. et al., Exp. Cell Res., 315: 542-555 (2009)

30 Summary of the Invention

Problem to be Solved by the Invention

35 [0010] Objects of the present invention are to identify a cancer antigen protein specifically expressed on the surface of a cancer cell and to provide the use of an antibody targeting the cancer antigen protein as an agent for treating and/or preventing a cancer.

Means for Solving the Problem

40 [0011] As a result of intensive studies, the present inventors have now obtained a cDNA encoding a protein that binds to an antibody existing in sera from dogs with breast cancer by the SEREX method using both cDNA libraries prepared from dog testis tissues and sera of dogs with breast cancer. The present inventors have now further prepared CAPRIN-1 proteins having the even-numbered amino acid sequences of SEQ ID NOS: 2 to 30 and antibodies against such CAPRIN-1 proteins based on the obtained dog gene and the corresponding human, cattle, horse, mouse, and chicken homologous genes. Thus, the present inventors have now found that CAPRIN-1 is specifically expressed in breast cancer, brain tumor, leukemia, lymphoma, lung cancer, uterine cervix cancer, bladder cancer, esophageal cancer, colorectal cancer, gastric cancer, and renal cancer cells, and that a portion of the CAPRIN-1 protein is specifically expressed on the surface of each cancer cell. The present inventors have thus now found that an antibody or antibodies against the portion of CAPRIN-1 expressed on the surface of each cancer cell is/are cytotoxic to the CAPRIN-1-expressing cancer cells. On the basis of these findings, the present invention as described below was completed.

45 [0012] The invention provides anti-CAPRIN-1 antibodies or fragments thereof, pharmaceutical compositions comprising the antibodies or fragments, pharmaceutical combinations, and products for medical use, all as defined in the claims.

Effects of the Invention

55 [0013] The antibody against CAPRIN-1 used in the present invention is cytotoxic to cancer cells. As such, the antibody against CAPRIN-1 is useful for treating or preventing cancers.

Brief Description of the Drawings

[0014]

- Fig. 1 shows the expression patterns of genes encoding CAPRIN-1 proteins in normal tissues and tumor cell lines. Reference No. 1 indicates the expression patterns of genes encoding CAPRIN-1 proteins, and Reference No. 2 indicates the expression patterns of GAPDH genes.
- Fig. 2 shows the cytotoxicity of an anti-CAPRIN-1 monoclonal antibody #1 (that is reactive with the surfaces of the cancer cells) against the MDA-MB-157 breast cancer cell line expressing CAPRIN-1. Reference No. 3 indicates the activity exhibited when the anti-CAPRIN-1 monoclonal antibody #1 was added. Reference No. 4 indicates the activity exhibited when PBS was added instead of the antibodies.
- Fig. 3 shows the anti-tumor effects of the anti-CAPRIN-1 monoclonal antibody #1 (that is reactive with the surfaces of cancer cells) against Balb/c mice into which the 4T1 mouse breast cancer cell line expressing CAPRIN-1 was transplanted. Reference No. 5 indicates the tumor size of a mouse to which the anti-CAPRIN-1 monoclonal antibody #1 was administered. Reference No. 6 indicates the tumor size of a mouse to which PBS was administered instead of the antibodies.

Mode for Carrying Out the Invention

- [0015] The anti-tumor activity of an antibody against a polypeptide represented by any of the even-numbered sequences of SEQ ID NOS: 2 to 30 used in the present invention can be evaluated by examining *in vivo* suppression of tumor growth in animals with cancer, or, examining whether or not the antibody exhibits cytotoxicity via immunocytes or complements to tumor cells expressing the polypeptide *in vitro*, as described later.
- [0016] In the context, the nucleotide sequences of polynucleotides encoding proteins comprising the even-numbered amino acid sequences (i.e., SEQ ID NOS: 2, , 4, , 6...28, 30) of SEQ ID NOS: 2 to 30 are represented by the odd-numbered sequences (i.e., SEQ ID NOS: 1, 3, 5...27, 29) of SEQ ID NOS: 1 to 29.
- [0017] The amino acid sequences that are represented by SEQ ID NOS: 6, 8, 10, 12, and 14 in the Sequence Listing disclosed herein are the amino acid sequences of CAPRIN-1 isolated as polypeptides, which bind to antibodies specifically existing in serum from a dog with cancer, through the SEREX method using a cDNA library from dog testis tissue and the serum of a dog with breast cancer. The amino acid sequences represented by SEQ ID NOS: 2 and 4 are the amino acid sequences of CAPRIN-1 isolated as human homologues. The amino acid sequence represented by SEQ ID NO: 16 is the amino acid sequence of CAPRIN-1 isolated as a cattle homologue. The amino acid sequence represented by SEQ ID NO: 18 is the amino acid sequence of CAPRIN-1 isolated as a horse homologue. The amino acid sequences represented by SEQ ID NOS: 20 to 28 are the amino acid sequences of CAPRIN-1 isolated as mouse homologues. The amino acid sequence represented by SEQ ID NO: 30 is the amino acid sequence of CAPRIN-1 isolated as a chicken homologue (see Example 1 described later). CAPRIN-1 is known to be expressed when normal cells in the resting phase are activated or give rise to cell division.
- [0018] It was known that CAPRIN-1 was not expressed on cell surfaces. However, as a result of the examination by the present inventors, it has now been revealed that a portion of the CAPRIN-1 protein is expressed on the surfaces of various cancer cells. It has thus been revealed that an antibody having immunological reactivity with a partial region of a CAPRIN-1 protein that is expressed on cancer cell surfaces or specifically recognizing the region (that is, specifically binding to the region) and comprising a heavy chain variable region that comprises SEQ ID NO: 39, 40, and 41 and a light chain variable region that comprises SEQ ID NO: 43, 44, and 45 exhibits anti-tumor activity.
- [0019] The above-described anti-CAPRIN-1 antibody used in the present invention may be any type of monoclonal antibody as long as it can exhibit anti-tumor activity. Examples of such an antibody include recombinant antibodies, such as a synthetic antibody, a multispecific antibody, a humanized antibody, a chimeric antibody, and a single chain antibody (scFv), a human antibody, and antibody fragments thereof, such as Fab, F(ab')₂, and Fv. These antibodies and fragments thereof can be prepared by methods known by persons skilled in the art. Also, when a subject is a human, human antibodies or humanized antibodies are desired in order to avoid or suppress rejection.
- [0020] The term "specifically binding to a partial region of a CAPRIN-1 protein" as used herein means that "the antibody specifically binds to a specific region of a CAPRIN-1 protein without substantially binding to protein portions other than such a region."
- [0021] The anti-tumor activity of an antibody that can be used in the present invention can be evaluated as described below by examining *in vivo* the suppression of the tumor growth in animals with cancer, or, by examining whether or not it exhibits *in vitro* an activity of cytotoxicity, which is mediated by immunocytes or complements, to tumor cells expressing the polypeptide.
- [0022] Furthermore, examples of the subject for cancer treatment and/or prevention in the present invention include mammals, such as humans, pet animals, domestic animals, and animals for competition. A preferable subject is a human.

[00223] Preparation of antigens and antibodies and pharmaceutical compositions relating to the present invention are described below.

<Preparation of antigens for antibody preparation>

[00241] Proteins or fragments thereof to be used as sensitizing antigens for obtaining anti-CAPRIN-1 antibodies used in the present invention may be derived from any animal species without particular limitation, such as humans, dogs, cattle, horses, mice, rats, and chickens. However, proteins or fragments thereof are preferably selected in consideration of compatibility with parent cells used for cell fusion. In general, mammal-derived proteins are preferred and, in particular, human-derived protein is preferred. For example, when CAPRIN-1 is human CAPRIN-1, the human CAPRIN-1 protein, a partial peptide thereof, or cells expressing human CAPRIN-1 can be used.

[00251] The nucleotide sequences and the amino acid sequences of human CAPRIN-1 and homologues thereof can be obtained by accessing GenBank (NCBI, U.S.A.) and using an algorithm such as BLAST or FASTA (Karlin and Altschul, Proc. Natl. Acad. Sci. U.S.A., 90: 5873-5877, 1993; Altschul et al., Nucleic Acids Res. 25: 3389-3402, 1997).

[00261] In the present invention, on the basis of the nucleotide sequence (SEQ ID NO: 1 or 3) or the amino acid sequence (SEQ ID NO: 2 or 4) of human CAPRIN-1, a target nucleic acid or a target protein comprises a sequence having 70% to 100%, preferably 80% to 100%, more preferably 90% to 100%, even more preferably 95% to 100% (e.g., 97% to 100%, 98% to 100%, 99% to 100%, or 99.5% to 100%) sequence identity with the nucleotide sequence or the amino acid sequence of the ORF or the mature portion of human CAPRIN-1. As used herein, the term "% sequence identity" refers to a percentage (%) of identical amino acids (or nucleotides) relative to the total number of amino acids (or nucleotides), when two sequences are aligned to achieve the highest similarity with or without introduction of gaps.

[00271] The length of a fragment of CAPRIN-1 protein ranges from the amino acid length of an epitope (antigenic determinant), which is the minimum unit recognized by an antibody, to a length less than the full length of the protein. The term "epitope" refers to a polypeptide fragment having antigenicity or immunogenicity in mammals, preferably in humans, and the minimum unit of the epitope consists of about 7 to 12 amino acids (e.g., 8 to 11 amino acids).

[00281] The polypeptides comprising the above-mentioned human CAPRIN-1 protein or partial peptides of the protein, can be synthesized by a chemical synthesis method, such as the Fmoc method (fluorenylmethyloxycarbonyl method) or the tBoc method (t-butyloxycarbonyl method) (Edited by The Japanese Biochemical Society, Seikagaku Jikken Koza (Biochemical Experimental Lecture Series) 1, Protein Chemistry IV, Chemical Modification and Peptide Synthesis, TOKYO KAGAKU DOZIN (Japan), 1981). Alternatively, the above-mentioned polypeptides may also be synthesized by conventional methods using various commercially available peptide synthesizers. Furthermore, with the use of known genetic engineering techniques (e.g., Sambrook et al., Molecular Cloning, 2nd Edition, Current Protocols in Molecular Biology (1989), Cold Spring Harbor Laboratory Press, Ausubel et al., Short Protocols in Molecular Biology, 3rd Edition, A compendium of Methods from Current Protocols in Molecular Biology (1995), John Wiley & Sons), a polynucleotide encoding the above polypeptide is prepared and then incorporated into an expression vector, which is subsequently introduced into a host cell in order to produce a polypeptide of interest in the host cell, and then recover it.

[00291] The polynucleotides encoding the above polypeptides can be easily prepared by known genetic engineering techniques or conventional techniques using a commercially available nucleic acid synthesizer. For example, DNA comprising the nucleotide sequence of SEQ ID NO: 1 can be prepared by PCR using a human chromosomal DNA or cDNA library, as a template, and a pair of primers designed to be able to amplify the nucleotide sequence represented by SEQ ID NO: 1. PCR conditions can be appropriately determined. For example, PCR conditions comprise conducting 30 cycles of the reaction cycle of: denaturation at 94°C for 30 seconds; annealing at 55°C for 30 seconds to 1 minute; and extension at 72°C for 2 minutes, using a thermostable DNA polymerase (e.g., Taq polymerase or Pfu polymerase) and PCR buffer containing Mg²⁺, followed by reacting at 72°C for 7 minutes. However, the PCR conditions are not limited to the above example. PCR techniques, conditions, and the like are described in Ausubel et al., Short Protocols in Molecular Biology, 3rd Edition, A compendium of Methods from Current Protocols in Molecular Biology (1995), John Wiley & Sons (particularly Chapter 15).

[00301] Also, on the basis of the nucleotide sequence and amino acid sequence information represented by SEQ ID NOS: 1 to 30 in the Sequence Listing described herein, appropriate probes or primers are prepared, and then a cDNA library of a human or the like is screened using them, so that desired DNA can be isolated. A cDNA library is preferably constructed from cells, organs or tissues, which express proteins having even-numbered sequences of SEQ ID NOS: 2 to 30. Examples of such cells or tissues include cells or tissues derived from testis, and cancers or tumors, such as leukemia, breast cancer, lymphoma, brain tumor, lung cancer, colorectal cancer, and the like. Procedures such as the preparation of probes or primers, construction of a cDNA library, screening of a cDNA library, and cloning of target genes are known by a person skilled in the art and can be carried out by the methods described in Sambrook et al., Molecular Cloning, 2nd Edition, Current Protocols in Molecular Biology (1989), Ausubel et al., (above), and the like. DNA encoding a human CAPRIN-1 protein or a partial peptide thereof can be obtained from the thus obtained DNA.

[00311] The host cells may be any cells, as long as they can express the above-mentioned polypeptide. Examples of

prokaryotic cells include, but are not limited to, *Escherichia coli* and the like. Examples of eukaryotic cells include, but are not limited to, mammalian cells, such as monkey kidney cells (COS1) and Chinese hamster ovary cells (CHO), human fetal kidney cell line (HEK293), fetal mouse skin cell line (NIH3T3), yeast cells such as budding yeast and fission yeast, silkworm cells, and *Xenopus* oocyte.

[0032] When prokaryotic cells are used as host cells, an expression vector used herein contains an origin replicable within prokaryotic cells, a promoter, a ribosome-binding site, a multiple cloning site, a terminator, a drug resistance gene, an auxotrophic complementary gene, and the like. Examples of *Escherichia coli* expression vector include a pUC-based vector, pBluescript II, a pET expression system, and a pGEX expression system. DNA encoding the above polypeptide is incorporated into such an expression vector, prokaryotic host cells are transformed with the vector, the thus obtained transformed cells are cultured, and thus the polypeptide encoded by the DNA can be expressed in prokaryotic host cells. At this time, the polypeptide can also be expressed as a fusion protein with another protein.

[0033] When eukaryotic cells are used as host cells, an expression vector used herein is an expression vector for eukaryotic cells, which contains a promoter, a splicing region, a poly(A) addition site, and the like. Examples of such an expression vector include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pcDNA3, and pYES2. In a manner similar to the above, DNA encoding the above polypeptide is incorporated into such an expression vector, eukaryotic host cells are transformed with the vector, the thus obtained transformed cells are cultured, and thus the polypeptide encoded by the DNA can be expressed in eukaryotic host cells. When pIND/V5-His, pFLAG-CMV-2, pEGFP-N1, pEGFP-C1, or the like is used as an expression vector, the above polypeptide can be expressed as a fusion protein to which a tag from among various tags such as a His tag (e.g., (His)₆-(His)₁₀), a FLAG tag, a myc tag, an HA tag, and GFP has been added.

[0034] For introduction of an expression vector into host cells, a known method can be employed, such as electroporation, a calcium phosphate method, a liposome method, a DEAE dextran method, microinjection, viral infection, lipofection, and binding to a cell membrane-permeable peptide.

[0035] The polypeptide of interest can be isolated and purified from host cells by a combination of known separation procedures. Examples of such procedures include, but are not limited to, treatment with a denaturing agent such as urea or a surfactant, ultrasonication, enzymatic digestion, salting-out or solvent fractionation and precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion exchange chromatography, hydrophobic chromatography, affinity chromatography, and reverse phase chromatography.

<Antibody structure>

[0036] An antibody is a heteromultimeric glycoprotein that generally contains at least two heavy chains and two light chains. Antibodies other than IgM is an about 150-kDa hetero tetramer glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. Typically, each light chain is connected to a heavy chain via one disulfide covalent bond, however, the number of disulfide bonds between heavy chains of various immunoglobulin isotypes is varied. Each heavy chain or each light chain also has an intrachain disulfide bond. Each heavy chain has a variable domain (VH region) on one end followed by several constant regions. Each light chain has a variable domain (VL region) and has one constant region on an end opposite to the other end. The constant region of a light chain is aligned with the first constant region of a heavy chain, and a light chain variable domain is aligned with a heavy chain variable domain.

A specific region of an antibody variable domain exhibits specific variability that is referred to as a complementarity determining region (CDR), so that it imparts binding specificity to the antibody. A portion of a variable region, which is relatively conserved, is referred to as a framework region (FR). Complete heavy chain and light chain variable domains separately contains four FRs ligated via three CDRs. The three CDRs in a heavy chain are referred to as CDRH1, CDRH2, and CDRH3 in this order from the N-terminus. Similarly, in the case of a light chain, CDRLs are referred to as CDRL1, CDRL2, and CDRL3. CDRH3 is most important for the binding specificity of an antibody to an antigen. Also, the CDRs of each chain are retained together in a state of being adjacent to each other due to the FR regions, contributing to the formation of the antigen binding site of the antibody together with CDRs from the other chain. A constant region does not directly contribute to the binding of an antibody to an antigen, but exhibits various effector functions, such as involvement in antibody-dependent cell-mediated cytotoxicity (ADCC), phagocytosis via binding to an Fcγ receptor, the rate of half-life/clearance via a neonate Fc receptor (FcRn), and complement-dependent cytotoxicity (CDC) via a C1q constituent of the complement cascade.

<Preparation of antibody >

[0037] The term "anti-CAPRIN-1 antibody" as used herein refers to an antibody having immunological reactivity with a full-length CAPRIN-1 protein or a fragment thereof.

[0038] As used herein, the term "immunological reactivity" refers to the property of *in vivo* binding of an antibody to a CAPRIN-1 antigen. Through such an *in vivo* binding, the function of damaging tumor (e.g., death, suppression, or

degeneration) is exhibited. Specifically, an antibody used in the present invention may be any type of antibody, as long as it binds to a CAPRIN-1 protein so as to be able to damage tumor, such as leukemia, lymphoma, breast cancer, brain tumor, lung cancer, bladder cancer, uterine cervix cancer, esophageal cancer, gastric cancer, renal cancer, or colorectal cancer.

[0039] In the present invention, examples of an antibody include, but are not particularly limited to, as long as it is a monoclonal antibody, a synthetic antibody, a multispecific antibody, a human antibody, a humanized antibody, a chimeric antibody, a single chain antibody, and an antibody fragment (e.g., Fab and F(ab')₂). Also, an antibody may be an immunoglobulin molecule of any class such as IgG, IgE, IgM, IgA, IgD, and IgY, or any subclass such as IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0040] The antibody may further be modified by, in addition to glycosylation, acetylation, formylation, amidation, phosphorylation, pegylation (PEG), or the like.

[0041] Preparation examples of various monoclonal antibodies are as described below.

[0042] When the antibody is a monoclonal antibody, for example, the breast cancer cell line SK-BR-3 expressing CAPRIN-1 is administered to a mouse for immunization, the spleen is removed from the mouse, cells are separated, and then the cells and mouse myeloma cells are fused. From among the thus obtained fusion cells (hybridomas), a clone producing an antibody having the effect of suppressing cancer cell proliferation is selected. A hybridoma producing a monoclonal antibody that has the effect of suppressing cancer cell proliferation is isolated, the hybridoma is cultured, and then an antibody is purified from the culture supernatant by general affinity purification, so that the antibody can be prepared.

[0043] The hybridoma producing a monoclonal antibody can also be prepared as described below, for example. First, an animal is immunized with a sensitizing antigen according to a known method. A general method is carried out by injecting a sensitizing antigen to a mammal intraperitoneally or subcutaneously. Specifically, a sensitizing antigen is diluted with PBS (Phosphate-Buffered Saline), saline, or the like to an appropriate amount, followed by suspension. The resultant is then mixed with an appropriate amount of a general adjuvant as necessary, such as Freund's complete adjuvant. After emulsification, the solution was administered to a mammal several times every 4 to 21 days. Furthermore, an appropriate carrier can also be used upon immunization with a sensitizing antigen.

[0044] A mammal is immunized as described above. After confirmation of a rise in a desired serum antibody level, immunized cells are collected from the mammal and then subjected to cell fusion. Preferable immunized cells are particularly splenocytes.

[0045] Mammalian myeloma cells are used as the other parent cells to be fused with the immunized cells. As the myeloma cells, various known cell lines are preferably used, 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).

[0046] Fusion of the immunized cell and the myeloma cell can be carried out according to basically a known method such as Kohler and Milstein's technique (Kohler, G and Milstein, C. Methods Enzymol. (1981) 73, 3-46), for example.

[0047] More specifically, the above cell fusion is carried out, for example, in the presence of a cell fusion accelerator in a usual nutrient culture medium. As this fusion accelerator, polyethyleneglycol (PEG), Sendai virus (HVJ), or the like is used. If desired, an auxiliary agent such as dimethylsulfoxide may be added and used in order to enhance fusion efficiency.

[0048] The ratio of the immunized cells to the myeloma cells to be used herein can be arbitrarily set. For example, the number of immunized cells that are preferably used is one to ten times the number of myeloma cells. As a culture medium to be used for the above-mentioned cell fusion, an RPMI1640 culture medium suitable for proliferation of the above-mentioned myeloma cell line, an MEM culture medium, and other culture media usually used for culturing this kind of cell can be used. Further, liquid that is supplemental to serum such as fetal bovine serum (FCS) can be used together therewith.

[0049] Cell fusion can be performed by thoroughly mixing the predetermined amounts of the above immunized cells and the myeloma cells in the above culture medium, and a PEG solution (for example, having an average molecular weight ranging from about 1000 to 6000) prewarmed at about 37°C is added usually at a concentration of 30%-60% (w/v) and mixed, thereby forming a culture containing hybridomas of interest. Next, a suitable culture medium is successively added to the thus-obtained culture, which is then centrifuged to remove the supernatant, and this procedure is repeated to remove the cell fusion agent or the like which is not preferable for the growth of hybridomas.

[0050] The thus obtained hybridomas are cultured for selection in a usual selection culture medium (e.g., a HAT culture medium containing hypoxanthine, aminopterin and thymidine). Culturing in this HAT culture medium is continued for a sufficient period of time (usually several days to several weeks) so that the cells (non-fused cells) other than the target hybridomas die. Subsequently, screening and single cloning of the hybridoma which produces an antibody of interest

are performed using the general limiting dilution method.

[0051] The above hybridomas are obtained by an immunizing non-human animal with an antigen. In addition to this method, hybridomas that produce a human antibody having desired activity (e.g., activity of suppressing cell proliferation) can also be obtained by *in vitro* sensitizing human lymphocytes, such as human lymphocytes that have been infected with the EB virus, with a protein, a protein-expressing cell, or a lysate thereof, followed by fusing of the thus sensitized lymphocytes with human-derived myeloma cells having an ability to permanently divide, such as U266 (Accession No. TIB 196).

[0052] The thus prepared hybridoma that produces a monoclonal antibody of interest can be passaged in a general culture medium and can be stored in liquid nitrogen over a long period of time.

[0053] Specifically, a hybridoma can be prepared by immunizing by a general immunization method using, as a sensitizing antigen, a desired antigen or a cell that expresses the desired antigen, fusing the thus obtained immunized cell with a known parent cell by a general cell fusion method, and then screening for a monoclonal antibody-producing cell (i.e., a hybridoma) by a general screening method.

[0054] As a human antibody-producing mouse, a KM mouse (Kirin Pharma/Medarex) and a Xeno mouse (Amgen) are known (e.g., International Patent Publications WO02/43478 and WO02/092812), for example. When such a mouse is immunized with a CAPRIN-1 protein or a fragment thereof, a complete human polyclonal antibody can be obtained from blood. Also, splenocytes are collected from the immunized mouse and then a human-type monoclonal antibody can be prepared by a method for fusion with myeloma cells.

[0055] An antigen can be prepared according to a method using animal cells (JP Patent Publication (Kohyo) No. 2007-530068) or baculovirus (e.g., International Patent Publication WO98/46777), for example. When an antigen has low immunogenicity, the antigen may be bound to a macromolecule having immunogenicity, such as albumin, and then immunization is carried out.

[0056] Furthermore, an antibody gene is cloned from said hybridoma and then incorporated into an appropriate vector. The vector is then introduced into a host, and then the genetically recombined antibody produced using gene recombination techniques can be used (e.g., see Carl, A. K. Borrebaeck, James, W. Larrick, THERAPEUTIC MONOCLONAL ANTIBODIES, Published in the United Kingdom by MACMILLAN PUBLISHERS LTD, 1990). Specifically, the cDNA of a variable region (V region) of an antibody is synthesized from the mRNA of the hybridoma using reverse transcriptase. When DNA encoding the V region of an antibody of interest can be obtained, this DNA is ligated to DNA encoding the constant region (C region) of a desired antibody, and then the resultant fusion product is incorporated into an expression vector. Alternatively, DNA encoding the V region of an antibody may be incorporated into an expression vector containing the DNA for the C region of an antibody. At this time, the DNA can be incorporated into an expression vector so that it is expressed under the control of expression control regions, such as enhancer and promoter. Next, host cells are transformed with the expression vector, so that the antibody can be expressed.

[0057] The anti-CAPRIN-1 antibody of the present invention is characterized by being a monoclonal antibody. Examples of a monoclonal antibody include human monoclonal antibodies, non-human animal monoclonal antibodies (e.g., a mouse monoclonal antibody, a rat monoclonal antibody, a rabbit monoclonal antibody, and a chicken monoclonal antibody), and chimeric monoclonal antibodies. A monoclonal antibody can be prepared by culturing a hybridoma obtained by cell fusion of a splenocyte from a non-human mammal (e.g., a mouse, a human antibody-producing mouse, a chicken, or a rabbit) immunized with a CAPRIN-1 protein, with a myeloma cell. A chimeric antibody is prepared by combining sequences from different animals, such as an antibody comprising heavy chain and light chain variable regions of a mouse antibody and heavy chain and light chain constant regions of a human antibody. A chimeric antibody can be prepared using a known method. For example, a chimeric antibody can be obtained by ligating DNA encoding an antibody V region to DNA encoding a human antibody C region, incorporating the resultant fusion product into an expression vector, and then introducing the vector into a host for production of the chimeric antibody. In Examples described later, human-chicken chimeric monoclonal antibodies were prepared and thus its anti-tumor effects were confirmed. These monoclonal antibodies comprise a heavy chain variable (VH) region comprising the amino acid sequence of SEQ ID NO: 42 and a light chain variable (VL) region comprising the amino acid sequence of SEQ ID NO: 46, wherein the VH region comprises CDR1 represented by the amino acid sequence of SEQ ID NO: 39, CDR2 represented by the amino acid sequence of SEQ ID NO: 40, and CDR3 represented by the amino acid sequence of SEQ ID NO: 41, and the VL region comprises CDR1 represented by the amino acid sequence of SEQ ID NO: 43, CDR2 represented by the amino acid sequence of SEQ ID NO: 44, and CDR3 represented by the amino acid sequence of SEQ ID NO: 45.

[0058] A humanized antibody is a modified antibody that is also referred to as a reshaped human antibody. A humanized antibody can be constructed by transplanting CDRs of an antibody from an immunized animal into the complementarity determining regions of a human antibody. General gene recombination techniques therefor are also known.

[0059] Specifically, DNA sequences designed to have each of the CDRs of a mouse or chicken antibody ligated to each of the framework regions (FRs) of a human antibody are synthesized by the PCR method from several oligonucleotides, which are prepared so as to have overlap portions at their terminal portions, for example. A humanized antibody can be obtained by ligating the thus obtained DNA to DNA encoding the constant region of a human antibody, incorporating

the resultant fusion product into an expression vector, introducing the vector into a host, and thus causing the host to produce the gene product (see European Patent Publication No. 239400 and International Patent Publication WO96/02576). As the FRs of a human antibody, which is ligated via CDRs, FRs that allow the formation of an antigen-binding site with good complementarity determining regions are selected. If necessary, for the formation of an antigen-binding site having the appropriate complementarity determining regions of a reshaped human antibody, the amino acids of the framework regions of an antibody variable region may be substituted (Sato, K. et al., Cancer Research, 1993, 53: 851-856). Also, the amino acids of FRs may be substituted with those of framework regions from various human antibodies (see International Patent Publication WO99/51743).

[0060] As the framework regions (FRs) of a human antibody, which are ligated via CDRs, FRs that allows the formation of an antigen-binding site with good complementarity determining regions are selected. If necessary, for the formation of an antigen-binding site having the appropriate complementarity determining regions of a reshaped human antibody, the amino acids of the framework regions of an antibody variable region may be substituted (Sato K. et al., Cancer Research 1993, 53: 851-856).

[0061] After preparation of a chimeric antibody or a humanized antibody, amino acids in a variable region (e.g., FR) or a constant region may be substituted with other amino acids.

[0062] Amino acid substitution is a substitution of, for example, less than 15, less than 10, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less amino acids and is preferably a substitution of 1 to 5 amino acids, and more preferably 1 or 2 amino acids. A substituted antibody should be functionally equivalent to an unsubstituted antibody. Substitution is desirably a substitution of a conservative amino acid(s) between amino acids having analogous properties such as electric charge, side chain, polarity, and aromaticity. Amino acids having analogous properties can be classified 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), for example.

[0063] Examples of a modified antibody product include antibodies bound to various molecules such as polyethylene glycol (PEG). Substances to be bound in the modified antibody product of the present invention are not limited. Such a modified antibody product can be obtained by subjecting the thus obtained antibody to chemical modification. Methods therefor have already been established in the art.

[0064] As used herein, the term "functionally equivalent" refers to that a subject antibody has biological or biochemical activity similar to that of the antibody of the present invention, and specifically refers to that a subject antibody has the function of impairing tumor without essentially causing rejection upon its application to a human, for example. An example of such activity includes an activity to suppress cell proliferation or a binding activity.

[0065] As a method well known by persons skilled in the art for preparation of a polypeptide functionally equivalent to a polypeptide, a method for introducing a mutation into a polypeptide is known. For example, persons skilled in the art can prepare an antibody functionally equivalent to the antibody of the present invention by appropriately introducing a mutation into the antibody using site-directed mutagenesis (Hashimoto-Gotoh, T. et al., (1995) Gene 152, 271-275; Zoller, MJ., and Smith, M. (1983) Methods Enzymol. 100, 468-500; Kramer, W. et al., (1984) Nucleic Acids Res. 12, 9441-9456; Kramer, W. and Fritz, HJ., (1987) Methods Enzymol. 154, 350-367; Kunkel, TA., (1985) Proc. Natl. Acad. Sci. U.S.A. 82, 488-492; Kunkel (1988) Methods Enzymol. 85, 2763-2766), for example.

[0066] An antibody that recognizes an epitope of a CAPRIN-1 protein recognized by the above anti-CAPRIN-1 antibody can be obtained by a method known by persons skilled in the art. For example, such an antibody can be obtained by a method that involves determining an epitope of a CAPRIN-1 protein recognized by an anti-CAPRIN-1 antibody, by a general method (e.g., epitope mapping) and then preparing an antibody using a polypeptide having an amino acid sequence contained in the epitope as an immunogen, or a method that involves determining an epitope of such an antibody prepared by a general method, and then selecting an antibody having the epitope identical with that of an anti-CAPRIN-1 antibody. As used herein, the term "epitope" refers to, in a mammal and preferably a human, a polypeptide fragment having antigenicity or immunogenicity. The minimum size unit thereof consists of about 7 to 12 amino acids, and preferably 8 to 11 amino acids.

[0067] 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 $5 \times 10^8 M^{-1}$, at least $10^9 M^{-1}$, at least $5 \times 10^9 M^{-1}$, at least $10^{10} M^{-1}$, at least $5 \times 10^{10} M^{-1}$, at least $10^{11} M^{-1}$, at least $5 \times 10^{11} M^{-1}$, at least $10^{12} M^{-1}$, or at least $10^{13} M^{-1}$.

[0068] The antibody of the present invention can be conjugated with an antitumor agent. Conjugation of the antibody with an antitumor agent can be carried out via a spacer having a group reactive with an amino group, a carboxyl group, a hydroxy group, a thiol group or the like (e.g., a succinimidyl succinate group, a formyl group, a 2-pyridyldithio group, a maleimidyl group, an alkoxy carbonyl group, and a hydroxy group).

[0069] Examples of the antitumor agent include the following known antitumor agents as in prior art literatures and the like, such as paclitaxel, doxorubicin, daunorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, thiotepa, busul-

fan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylolmelamine, bullatacin, bullatacinone, camptothecin, bryostatins, callistatin, cryptophycin1, cryptophycin8, dolastatin, duocarmycin, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlomaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, dynemicin, clodronate, esperamicin, aclacinomycin, actinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabacin, carminomycin, carzinophilin, chromomycin, dactinomycin, detorbin, 6-diazo-5-oxo-L-norleucine, adriamycin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycinC, 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, floxuridine, androgens (e.g., calusterone, dromostanolone propionate, epitostanol, mepitiostane, and testolactone), aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone, aldophosphamideglycoside, aminolaevulinic acid, eniluracil, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, lenthinan, lonidamine, maytansine, ansamitocine, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethyl hydrazide, procarbazine, razoxane, rhizoxin, schizophyllan, spirogermanium, tenuazonic acid, triaziquone, roridine A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, docetaxel, chlorambucil, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, oxaliplatin, carboplatin, vinblastine, etoposide, ifosfamide, mitoxanthrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, irinotecan, topoisomerase inhibitor, difluoromethylolnitrine (DMFO), retinoic acid, capecitabine, and pharmaceutically acceptable salts or derivatives thereof.

[0070] Through administration of the antibody of the present invention in combination with an antitumor agent, even higher therapeutic effects can be obtained. This technique is applicable to both before and after surgery of a cancer patient with the expression of CAPRIN-1. Particularly after surgery, more effective prevention of cancer recurrences or prolonged survival period can be obtained against cancer with the expression of CAPRIN-1, which has been conventionally treated with an antitumor agent alone.

[0071] Examples of the antitumor agent to be administered in combination with the antibody of the present invention include the following known antitumor agents as in prior art literatures or the like, such as paclitaxel, doxorubicin, daunorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, thiotepa, busulfan, improsulfan, piposulfan, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylolmelamine, bullatacin, bullatacinone, camptothecin, bryostatins, callistatin, cryptophycin1, cryptophycin8, dolastatin, duocarmycin, eleutherobin, pancratistatin, sarcodictyin, spongistatin, chlorambucil, chlomaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, calicheamicin, dynemicin, clodronate, esperamicin, aclacinomycin, actinomycin, anthramycin, azaserine, bleomycin, cactinomycin, carabacin, carminomycin, carzinophilin, chromomycin, dactinomycin, detorbin, 6-diazo-5-oxo-L-norleucine, adriamycin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycinC, 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, floxuridine, calusterone, dromostanolone propionate, epitostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolic acid, aceglatone, aldophosphamideglycoside, aminolaevulinic acid, eniluracil, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, elfornithine, elliptinium acetate, epothilone, etoglucid, lenthinan, lonidamine, maytansine, ansamitocine, mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethyl hydrazide, procarbazine, razoxane, rhizoxin, schizophyllan, spirogermanium, tenuazonic acid, triaziquone, roridine A, anguidine, urethane, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, docetaxel, chlorambucil, gemcitabine, 6-thioguanine, mercaptopurine, cisplatin, oxaliplatin, carboplatin, vinblastine, etoposide, ifosfamide, mitoxanthrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, irinotecan, topoisomerase inhibitor, difluoromethylolnitrine (DMFO), retinoic acid, capecitabine, and pharmaceutically acceptable (known) salts or (known) derivatives thereof. Of the above examples, particularly cyclophosphamide, paclitaxel, docetaxel, and vinorelbine are preferably used.

[0072] Alternatively, a known radio isotope as in prior art literatures or the like, such as ^{211}At , ^{131}I , ^{125}I , ^{90}Y , ^{186}Re , ^{188}Re , ^{153}Sm , ^{212}Bi , ^{32}P , ^{175}Lu , or ^{176}Lu can be bound to the antibody of the present invention. A desired radio isotope is effective for treatment or diagnosis of tumor.

[0073] The antibody of the present invention is an antibody having immunological reactivity with CAPRIN-1, or, an antibody specifically binding to CAPRIN-1, which exhibits cytotoxic activity against cancer or the effect of suppressing

tumor growth. The antibody should have a structure such that rejection is almost or completely avoided in a subject animal to which the antibody is administered. Examples of such an antibody include, when a subject animal is a human, a human antibody, a humanized antibody, a chimeric antibody (e.g., a human-mouse chimeric antibody), a single chain antibody, and a bispecific antibody. These antibodies are: recombinant antibodies in which heavy chain and light chain variable regions are from a human antibody; recombinant antibodies in which heavy chain and light chain variable regions comprise complementarity determining regions (CDRs) (CDR1, CDR2, and CDR3) from a non-human animal antibody and framework regions from a human antibody; or recombinant antibodies in which heavy chain and light chain variable regions are from a non-human animal antibody, and, heavy chain and light chain constant regions are from a human antibody. Preferable antibodies are the former two antibodies.

[0074] These recombinant antibodies can be prepared as follows by cloning DNA encoding an anti-human CAPRIN-1 monoclonal antibody (e.g., a human monoclonal antibody, a mouse monoclonal antibody, a rat monoclonal antibody, a rabbit monoclonal antibody, or a chicken monoclonal antibody) from an antibody-producing cell such as a hybridoma, preparing DNA encoding a light chain variable region and a heavy chain variable region of the antibody by an RT-PCR method using it as a template, and then determining the sequence of each variable region of light chain and heavy chain or each sequence of CDR1, CDR2, and CDR3 based on a 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)).

[0075] Furthermore, DNA encoding each of these variable regions or DNA encoding each CDR is prepared using gene recombination techniques (Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1989)) or a DNA synthesizer. Here, the above human monoclonal antibody-producing hybridoma can be prepared by immunizing a human antibody-producing animal (e.g., a mouse) with human CAPRIN-1 and then fusing splenocytes excised from the immunized animal to myeloma cells. Alternatively, DNAs encoding a light chain or heavy chain variable region and a constant region from a human antibody are prepared as necessary using gene recombination techniques or a DNA synthesizer.

[0076] In the case of humanized antibody, DNA is prepared by substituting a CDR coding sequence in DNA encoding a variable region of light chain or heavy chain derived from a human antibody, with a CDR coding sequence corresponding thereto of an antibody derived from a non-human animal (e.g., a mouse, a rat, or a chicken) and then ligating the DNA thus obtained to DNA encoding a constant region of light chain or heavy chain derived from a human antibody. Thus, DNA encoding humanized antibody can be prepared.

[0077] In the case of chimeric antibody, DNA encoding a chimeric antibody can be prepared by ligating DNA encoding a light chain or heavy chain variable region of an antibody from a non-human animal (e.g., a mouse, a rat, and a chicken) to DNA encoding a light chain or heavy chain constant region from a human antibody.

[0078] In the case of single chain antibody, this antibody is an antibody prepared by linearly ligating a heavy chain variable region to a light chain variable region via a linker. Thus, DNA encoding a single chain antibody can be prepared by binding DNA encoding a heavy chain variable region, DNA encoding a linker, and DNA encoding a light chain variable region. Herein, a heavy chain variable region and a light chain variable region are both from a human antibody, or, only CDRs are substituted with CDRs of an antibody from a non-human animal (e.g., a mouse, a rat, and a chicken) although the other regions are from a human antibody. Also, a linker comprises 12 to 19 amino acids, such as (G₄S)₃ of 15 amino acids (G. -B. Kim et al., Protein Engineering Design and Selection 2007, 20 (9): 425-432).

[0079] In the case of bispecific antibody (diabody), this antibody is capable of specifically binding to two different epitopes. For example, DNA encoding a bispecific antibody can be prepared by linking DNA encoding a heavy chain variable region A, DNA encoding a light chain variable region B, DNA encoding a heavy chain variable region B, and DNA encoding a light chain variable region A in this order (here, DNA encoding a light chain variable region B is bound to DNA encoding a heavy chain variable region B via DNA encoding the above linker). Here, a heavy chain variable region and a light chain variable region are both from a human antibody, or, only CDRs are substituted with CDRs of an antibody from a non-human animal (e.g., a mouse, a rat, or a chicken) although the other regions are from a human antibody.

[0080] The above-prepared recombinant DNA is incorporated into one or a plurality of appropriate vectors, they are introduced into host cells (e.g., mammalian cells, yeast cells, or insect cells), and then (co)expression is caused, so that a recombinant antibody can be prepared (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).

[0081] Examples of the antibody of the present invention prepared by the above method include an antibody comprising a heavy chain variable region comprising SEQ ID NOS: 39, 40, and 41 and a light chain variable region comprising SEQ ID NOS: 43, 44, and 45 (e.g., the antibody composed of the heavy chain variable region of SEQ ID NO: 42 and the light chain variable region of SEQ ID NO: 46).

[0082] The amino acid sequences represented by SEQ ID NOS: 39, 40, and 41 are CDR1, CDR2, and CDR3 of a chicken antibody heavy chain variable region. Also, the amino acid sequences represented by SEQ ID NOS: 43, 44, and 45 are CDR1, CDR2, and CDR3 of a chicken antibody light chain variable region, respectively.

[0083] Also, the humanized antibody, the chimeric antibody, the single chain antibody, or the bispecific antibody of the present invention is the following antibody, for example:

[0084]

(i) an antibody wherein a heavy chain variable region comprises the amino acid sequences of SEQ ID NOS: 39, 40, and 41 and the amino acid sequences of framework regions from a human antibody, and, a light chain variable region comprises the amino acid sequences of SEQ ID NOS: 43, 44, and 45 and the amino acid sequences of framework regions from a human antibody (e.g., the antibody wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 42, and, the light chain variable region comprises the amino acid sequence of SEQ ID NO: 46); and **[0088]**

(ii) an antibody wherein a heavy chain variable region comprises the amino acid sequences of SEQ ID NOS: 39, 40, and 41 and the amino acid sequences of framework regions from a human antibody, and, a heavy chain constant region comprises an amino acid sequence from a human antibody, and, a light chain variable region comprises the amino acid sequences of SEQ ID NOS: 43, 44, and 45 and the amino acid sequences of framework regions from a human antibody, and a light chain constant region comprises an amino acid sequence from a human antibody (e.g., the antibody wherein a heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 42, and, a heavy chain constant region comprises an amino acid sequence from a human antibody, as well as, a light chain variable region comprises the amino acid sequence of SEQ ID NO: 46, and, a light chain constant region comprises an amino acid sequence from a human antibody).

[0085] In addition, the sequences of human antibody heavy chain and light chain constant regions and variable regions can be obtained from NCBI (e.g., U.S.A.: GenBank, UniGene), for example. For example, the sequence of Accession No. J00228 can be referred to as a human IgG1 heavy chain constant region, the sequence of Accession No. J00230 can be referred to as a human IgG2 heavy chain constant region, the sequence of Accession No. X03604 can be referred to as a human IgG3 heavy chain constant region, the sequence of Accession No. K01316 can be referred to as a human IgG4 heavy chain constant region, the sequences of Accession No. V00557, X64135, X64133, and the like can be referred to as human light chain κ constant regions, and the sequences of registration nos. X64132, X64134, and the like can be referred to as human light chain λ constant regions.

[0086] The above antibodies preferably have cytotoxic activity and thus can exhibit anti-tumor effects.

[0087] Also, the specific sequences of heavy chain and light chain variable regions or CDRs in the above antibodies are given simply for illustrative purposes, and thus are clearly not limited to such specific sequences. A hybridoma capable of producing another human antibody or non-human animal antibody (e.g., a mouse antibody) against human CAPRIN-1 is prepared, a monoclonal antibody that is produced by the hybridoma is collected, and then whether or not it is a target antibody is determined by immunological binding property with human CAPRIN-1 and cytotoxic activity as indicators. After identification of a hybridoma producing the target monoclonal antibody in this manner, DNA encoding heavy chain and light chain variable regions of the target antibody is prepared from the hybridoma as described above, sequencing is carried out, and then the DNA is used for preparation of another antibody.

[0088] Furthermore, the above antibody of the present invention, the sequence of each of the above antibodies, particularly the sequence of the framework region and/or the sequence of the constant region may have a substitution, a deletion, or an addition of one or several (preferably, 1 or 2) amino acids, as long as it has specificity for specific recognition of CAPRIN-1. Here the term "several" refers to 2 to 5, and preferably 2 or 3.

[0089] The present invention further provides DNA encoding the above antibody of the present invention, or, DNA encoding the above antibody heavy chain or light chain, or, DNA encoding the above antibody heavy chain or light chain variable region. Examples of such DNA include, DNA encoding a heavy chain variable region comprising the nucleotide sequences encoding the amino acid sequences of SEQ ID NOS: 39, 40, and 41 and DNA encoding a light chain variable region comprising the nucleotide sequences encoding the amino acid sequences of SEQ ID NOS: 43, 44, and 45.

[0090] Complementarity determining regions (CDRs) encoded by the sequences of DNA are regions for determining the specificity of an antibody. Thus, sequences encoding regions in an antibody other than CDRs (specifically, a constant region and a framework region) may be from other antibodies. Here, examples of such "other antibodies" include antibodies from non-human organisms, and are preferably from a human in view of reduction of side effects. Thus, in the case of the above DNA, regions encoding each framework region and each contact region of heavy chains and light chains preferably comprise nucleotide sequences encoding corresponding amino acid sequences from a human antibody.

[0091] Further alternative examples of DNA encoding the antibody of the present invention include DNA encoding a heavy chain variable region comprising the nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 42 and DNA in which the region encoding a light chain variable region comprises the nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 46. Here, an example of the nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 42 is the nucleotide sequence of SEQ ID NO: 49. Also, an example of the nucleotide sequence encoding

the amino acid sequence of SEQ ID NO: 46 is the nucleotide sequence of SEQ ID NO: 50. In these DNAs, regions encoding each constant region of heavy chains and light chains preferably comprise nucleotide sequences encoding the corresponding amino acid sequences from a human antibody.

[0092] The DNA of the present invention can be obtained by the above methods or the following method, for example.

First, total RNA is prepared from a hybridoma relating to the antibody of the present invention using a commercially available RNA extraction kit, and then cDNA is synthesized with reverse transcriptase using random primers, and the like. Subsequently, cDNA encoding an antibody is amplified by a PCR method using as primers the oligonucleotides of sequences conserved in each variable region of known mouse antibody heavy chain and light chain genes. The sequence encoding a constant region can be obtained by amplifying a known sequence by a PCR method. The nucleotide sequence of DNA can be determined by a conventional method such as insertion of it into a plasmid or a phage for sequencing.

[0093] An anti-CAPRIN-1 antibody to be used in the present invention is considered to exhibit the anti-tumor effects against CAPRIN-1-expressing cancer cells through the following mechanism.

[0094] Antibody-dependent cytotoxic activity (ADCC) of effector cells against CAPRIN-1-expressing cells, and the complement-dependent cytotoxicity (CDC) against CAPRIN-1-expressing cells.

[0095] Therefore, the activity of an anti-CAPRIN-1 antibody to be used in the present invention can be evaluated by, as specifically described in Examples below, measuring *ex vivo* the above ADCC activity or CDC activity against CAPRIN-1-expressing cancer cells.

[0096] An anti-CAPRIN-1 antibody to be used in the present invention binds to a CAPRIN-1 protein on a cancer cell and exhibits anti-tumor effects due to the above activity, and thus it is useful for treating or preventing cancer. Specifically, the present invention provides a pharmaceutical composition for treating and/or preventing a cancer, which comprises an anti-CAPRIN-1 antibody as an active ingredient. When the anti-CAPRIN-1 antibody is used for administration thereof to a human body (antibody therapy), it is preferably human antibody or humanized antibody in order to decrease immunogenicity.

[0097] In addition, the higher the binding affinity between an anti-CAPRIN-1 antibody and a CAPRIN-1 protein on the cancer cell surfaces, the stronger the anti-tumor activity of the anti-CAPRIN-1 antibody that can be obtained. Therefore, when an anti-CAPRIN-1 antibody having high binding affinity with a CAPRIN-1 protein can be acquired, stronger anti-tumor effects can be expected and such antibody's application as a pharmaceutical composition for the purpose of cancer treatment and/or prevention becomes possible. Such high binding affinity is desirably as follows. As described above, binding constant (affinity constant) K_a (k_{on}/k_{off}) is preferably at least 10^7 M⁻¹, at least 10^8 M⁻¹, at least 5×10^8 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, or, at least 10^{13} M⁻¹.

<Binding to antigen-expressing cell>

[0098] The capacity of an antibody to bind to CAPRIN-1 can be specified by binding assay using ELISA, a Western blot method, immuno-fluorescence and flow cytometric analysis, or the like as described in Examples.

<Immunohistochemical staining>

[0099] An antibody that recognizes CAPRIN-1 can be tested for reactivity to CAPRIN-1 by a method for immunohistochemistry known by persons skilled in the art using paraformaldehyde- or acetone-fixed frozen sections or paraformaldehyde-fixed paraffin-embedded tissue sections, which is prepared from tissue samples obtained from a patient during surgery, or tissue samples obtained from an animal having heterotransplant tissue inoculated with a cell line expressing CAPRIN-1, naturally or after transfection.

[0100] An antibody reactive with CAPRIN-1 can be stained by various methods for immunohistochemical staining. For example, a horseradish peroxidase-conjugated goat anti-mouse antibody or goat anti-chicken antibody is caused to undergo reaction, a target antibody can be visualized.

<Pharmaceutical composition>

[0101] A target of the pharmaceutical composition for treating and/or preventing a cancer of the present invention is not particularly limited, as long as it is a cancer (cell) expressing a CAPRIN-1 gene.

[0102] The term "tumor" and "cancer" as used herein refers to malignant neoplasm and is used interchangeably.

[0103] Cancer to be subjected to the present invention is cancer expressing genes encoding CAPRIN-1 proteins having amino acid sequences of even-numbered SEQ ID NOS: 2 to 30. Examples of such cancer include preferably breast cancer, brain tumor, leukemia, lung cancer, lymphoma, mastocytoma, renal cancer, uterine cervix cancer, bladder cancer, esophageal cancer, gastric cancer, and colorectal cancer.

[0104] Examples of such specific cancer include, but are not limited to, breast adenocarcinoma, composite type breast

adenocarcinoma, mammary gland malignant mixed tumor, intraductal papillary adenocarcinoma, lung adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, glioma that is neural epithelial tissue tumor, ependymoma, neurocytoma, fetal neuroectodermal tumor, schwannoma, neurofibroma, meningioma, chronic lymphocytic leukemia, lymphoma, gastrointestinal lymphoma, digestive lymphoma, small-cell to medium-cell lymphoma, cancer of cecum, ascending colon cancer, descending colon cancer, transverse colon cancer, sigmoid colon cancer, and rectal cancer.

[0105] Moreover, preferable subjects are mammals including primates, pet animals, domestic animals, animals for race, and the like and are particularly preferably humans, dogs, and cats.

[0106] When an antibody to be used in the present invention is used as a pharmaceutical composition, it can be formulated by a method known by persons skilled in the art. For example, the antibody can be used parenterally in the form of an injection preparation such as an aseptic solution or a suspension prepared with water or a pharmacologically acceptable solution other than water. For example, it can be formulated by mixing in a unit dosage form required by generally accepted pharmaceutical practice in appropriate combination with a pharmacologically acceptable carrier or medium, specifically, sterile water or saline, vegetable oil, an emulsifier, a suspension, a surfactant, a stabilizer, a flavoring compound, an excipient, a vehicle, an antiseptic, a binder, and the like. The amounts of active ingredients in these preparations are determined so that an appropriate dose within the indicated range can be obtained.

[0107] An aseptic composition for injection can be prescribed according to general pharmaceutical practice using a vehicle such as distilled water for injection.

[0108] Examples of an aqueous solution for injection include saline, an isotonic solution containing dextrose or other adjuvants, such as D-sorbitol, D-mannose, D-mannitol, and sodium chloride. These examples may be used in combination with an appropriate solubilizing agent such as alcohol, specifically ethanol and polyalcohol (e.g., propylene glycol and polyethylene glycol), and nonionic surfactant (e.g., polysorbate 80 (TM) and HCO-60).

[0109] Examples of the oil include sesame oil and soybean oil, which can be used in combination with a solubilizing agent such as benzyl benzoate or benzyl alcohol. Also, a buffering agent such as phosphate buffer or sodium acetate buffer, a soothing agent such as procaine hydrochloride, a stabilizer such as benzyl alcohol or phenol, and an antioxidant may be combined therewith. An appropriate ampul is generally filled with the thus prepared injection solution.

[0110] Administration is peroral or perenteral administration and is preferably perenteral administration. Specific examples of the route of administration include injection, transnasal administration, pulmonary administration, and transdermal administration. Examples of injection include intravenous injection, intramuscular injection, intraperitoneal injection, and subcutaneous injection, so that systemic or local administration is possible.

[0111] Also, administration methods can be appropriately selected depending on a patient's age, body weight, gender, symptoms, and the like. The dosage per administration of a pharmaceutical composition containing an antibody or a polynucleotide encoding the antibody can be selected from the range between 0.0001 mg and 1000 mg per kg of body weight, for example. Alternatively, for example, dosage can be selected from the range between 0.001 mg/body and 100000 mg/body per patient. However, the dosage range is not always limited to these numerical values. The dosage and administration method are varied depending on a patient's body weight, age, gender, symptoms, and the like, but can be appropriately selected by persons skilled in the art.

[0112] The above pharmaceutical composition containing the antibody or a fragment thereof of the present invention is administered to a subject, so that cancer, preferably, breast cancer, brain tumor, leukemia, lung cancer, lymphoma, mastocytoma, renal cancer, uterine cervix cancer, bladder cancer, esophageal cancer, gastric cancer, and colorectal cancer can be treated and/or prevented.

[0113] The present invention further encompasses means, as defined in the claims, for treating and/or preventing a cancer, by administering to a subject the pharmaceutical composition of the present invention in combination with the above exemplified antitumor agent or pharmaceutical composition containing such antitumor agent. The antibody or a fragment thereof of the present invention and an antitumor agent may be administered simultaneously or separately to a subject. They can be separately administered regardless of the order of administration. The administration intervals, dosage, the route of administration, and the frequency of administration can be appropriately selected by a specialist. Examples of the other pharmaceutical formulation to be administered simultaneously include pharmaceutical compositions obtained by mixing the antibody or a fragment thereof of the present invention with an antitumor agent in a pharmacologically acceptable carrier (or a medium) followed by formulation. Furthermore, about either the above pharmaceutical composition containing an antitumor agent and formulation, explanations concerning prescription, formulation, the route of administration, dose, cancer, and the like for administering a pharmaceutical composition containing the antibody of the present invention and formulation are applicable.

[0114] Therefore, the present invention also provides a pharmaceutical combination for treating and/or preventing a cancer, comprising the pharmaceutical composition of the present invention, and the above exemplified pharmaceutical composition containing an antitumor agent.

[0115] Also, the present invention provides a pharmaceutical composition for treating and/or preventing a cancer, comprising the antibody or a fragment thereof of the present invention and an antitumor agent together with a pharma-

cologically acceptable carrier.

<Polypeptide and DNA>

[0116] The following polypeptides and DNAs relating to the above antibodies are also disclosed.

(i) A polypeptide comprising the amino acid sequence of SEQ ID NO: 42 and DNA encoding the polypeptide, wherein the DNA comprises the nucleotide sequence of SEQ ID NO: 49.

(ii) A polypeptide comprising the amino acid sequence of SEQ ID NO: 46 and DNA encoding the polypeptide, wherein the DNA comprises the nucleotide sequence of SEQ ID NO: 50.

(iii) A heavy chain CDR polypeptide consisting of the amino acid sequences represented by SEQ ID NOS: 39, 40, and 41, and DNA encoding the polypeptide.

(iv) A light chain CDR polypeptide consisting of the amino acid sequences represented by SEQ ID NOS: 43, 44, and 45, and DNA encoding the polypeptide.

[0117] These polypeptides and DNAs can be prepared using gene recombination techniques as described above.

Examples

[0118] The present invention is described more specifically based on Examples, but the scope of the present invention is not limited by these specific examples.

Example 1 Identification of novel cancer antigen protein by SEREX method

(1) Preparation of cDNA library

[0119] Total RNA was extracted from a testis tissue of a healthy dog by an acid guanidium-phenol-chloroform method. PolyA RNA was purified according to protocols included with an Oligotex-dT30 mRNA purification Kit (Takara Shuzo Co., Ltd.) using the kit.

[0120] A dog testis cDNA phage library was synthesized using the thus obtained mRNA (5 µg). For preparation of the cDNA phage library, a cDNA synthesis kit, a ZAP-cDNA synthesis kit, and a ZAP-cDNA gigapack III gold cloning kit (STRATAGENE) were used and the library was prepared according to protocols included with the kit. The size of the thus prepared cDNA phage library was 7.73×10^5 pfu/ml.

(2) Screening of cDNA library using serum

[0121] Immunoscreening was carried out using the above-prepared dog testis cDNA phage library. Specifically, host *Escherichia coli* (XL1-Blue MRF') was infected with the phage so that 2210 clones were present on a $\phi 90 \times 15$ mm NZY agarose plate. Cells were cultured at 42°C for 3 to 4 hours, so as to cause plaque formation. The plate was covered with a nitrocellulose membrane (Hybond C Extra: GE HealthCare Bio-Sciences) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours. Proteins were induced, expressed, and then transferred to the membrane. Subsequently, the membrane was recovered, immersed, and shaken in TBS (10 mM Tris-HCl, 150 mM NaCl pH 7.5) containing 0.5% powdered skim milk at 4°C overnight, so that nonspecific reaction was suppressed. The filter was caused to react with 500-fold diluted sera of dogs with cancer at room temperature for 2 to 3 hours.

[0122] As the above sera from dogs with cancer, sera collected from dogs with breast cancer were used. The sera were stored at -80°C and then subjected to pretreatment immediately before use. Pretreatment for sera was performed by the following method. Specifically, host *Escherichia coli* (XL1-Blue MRF') was infected with λ ZAP Express phage into which no foreign gene had been inserted, and then cultured on NZY plate medium at 37°C overnight. Subsequently, a 0.2 M NaHCO₃ buffer (pH 8.3) containing 0.5 M NaCl was added to the plate and then the plate was left to stand at 4°C for 15 hours. The supernatants were collected as *Escherichia coli*/phage extracts. Next, the collected *Escherichia coli*/phage extract was passed through a NHS-column (GE HealthCare Bio-Sciences), so as to immobilize the *Escherichia coli*-phage-derived protein. The serum of a dog with cancer was passed through the column to which the protein had been immobilized for reaction, thereby removing *Escherichia coli* and antibodies adsorbed to the phage from the serum. Each serum fraction that had passed through the column was diluted 500-fold with TBS containing 0.5% powdered skim milk, and the resultant was used as an immunoscreening material.

[0123] A membrane, to which the thus treated serum and the fusion protein had been blotted, was washed 4 times with TBS-T (0.05% Tween20/TBS). The membrane was reacted with goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated: BETHYL Laboratories) diluted 5000-fold as a secondary antibody with TBS containing 0.5% powdered skim

milk at room temperature for 1 hour. Detection was carried out by enzyme color reaction using an NBT/BCIP reaction solution (Roche). Colonies corresponding to the color reaction positive site were collected from the $\phi 90 \times 15$ mm NZY agarose plate, and then dissolved in 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO₄, 50 mM Tris-HCl, 0.01% gelatin, pH 7.5). Until unification of color reaction positive colonies, secondary screening and tertiary screening were repeated by a method similar to the above. Thus, 30940 phage clones that had reacted with serum IgG were screened so that 5 positive clones were isolated.

(3) Homology search for isolated antigen gene

[0124] A procedure for conversion of phage vectors to plasmid vectors was performed for the 5 positive clones isolated by the above method for the purpose of subjecting the clones to nucleotide sequence analysis. Specifically, 200 μ l of a solution of host *Escherichia coli* (XL1-Blue MRF⁺) prepared to give an absorbance OD₆₀₀ of 1.0, 250 μ l of a purified phage solution, and 1 μ l of ExAssist helper phage (STRATAGENE) were mixed and allowed to react at 37°C for 15 minutes. After that, 3 ml of LB medium was added, cells were cultured at 37°C for 2.5 to 3 hours, and then the resultant was immediately put in water bath at 70°C for incubation for 20 minutes. Centrifugation was carried out at 4°C, 1000 x g for 15 minutes, and then the supernatant was collected as a phagemid solution. Subsequently, 200 μ l of a solution prepared from phagemid host *Escherichia coli* SOLR to give an absorbance OD₆₀₀ of 1.0 and 10 μ l of the purified phage solution were mixed, followed by 15 minutes of reaction at 37°C. 50 μ l of the resultant was plated on LB agar medium containing ampicillin (at final concentration of 50 μ g/ml) and then cultured overnight at 37°C. A single colony of transformed SOLR was collected and then cultured on LB medium containing ampicillin (at final concentration of 50 μ g/ml) at 37°C. After culture, plasmid DNA carrying an insert of interest was purified using a QIAGEN plasmid Miniprep Kit (QIAGEN).

[0125] The purified plasmid was subjected to the analysis of the entire sequence of the insert by the primer walking method using the T3 primer of SEQ ID NO: 31 and the T7 primer of SEQ ID NO: 32. The gene sequences of SEQ ID NOS: 5, 7, 9, 11, and 13 were obtained by the sequence analysis. With the use of the nucleotide sequences of the genes and the amino acid sequences thereof (SEQ ID NOS: 6, 8, 10, 12, and 14), homology search program BLAST search (<http://www.ncbi.nlm.nih.gov/BLAST>) was conducted for searching homology with known genes. As a result, it was revealed that all the five obtained genes were genes encoding CAPRIN-1. The sequence identities among the five genes were 100% at the nucleotide sequence level and 99% at the amino acid sequence level in the regions to be translated into proteins. The sequence identities of these genes and the human homologue-encoding gene were 94% at the nucleotide sequence level and 98% at the amino acid sequence level in the regions to be translated into proteins. The nucleotide sequences of the human homologues are represented by SEQ ID NOS: 1 and 3 and the amino acid sequences of the same are represented by SEQ ID NOS: 2 and 4. Also, the sequence identities of the obtained dog genes and the cattle homologue-encoding gene were 94% at the nucleotide sequence level and 97% at the amino acid sequence level in the regions to be translated into proteins. The nucleotide sequence of the cattle homologue is represented by SEQ ID NO: 15 and the amino acid sequence of the same is represented by SEQ ID NO: 16. In addition, the sequence identities of the human homologue-encoding genes and the cattle homologue-encoding gene were 94% at the nucleotide sequence level and 93% to 97% at the amino acid sequence level in the regions to be translated into proteins. Also, the sequence identities of the obtained dog genes and the horse homologue-encoding gene were 93% at the nucleotide sequence level and 97% at the amino acid sequence level in the regions to be translated into proteins. The nucleotide sequence of the horse homologue is represented by SEQ ID NO: 17 and the amino acid sequence of the same is represented by SEQ ID NO: 18. In addition, the sequence identities of the human homologue-encoding genes and the horse homologue-encoding gene were 93% at the nucleotide sequence level and 96% at the amino acid sequence level in the regions to be translated into proteins. Also, the sequence identities of the obtained dog genes and the mouse homologue-encoding genes were 87% to 89% at the nucleotide sequence level and 95% to 97% at the amino acid sequence level in the regions to be translated into proteins. The nucleotide sequences of the mouse homologues are represented by SEQ ID NOS: 19, 21, 23, 25, and 27 and the amino acid sequences of the same are represented by SEQ ID NOS: 20, 22, 24, 26, and 28. In addition, the sequence identities of the human homologue-encoding genes and the mouse homologue-encoding genes were 89% to 91% at the nucleotide sequence level and were 95% to 96% at the amino acid sequence level in the regions to be translated into proteins. Also, the sequence identities of the obtained dog genes and the chicken homologue-encoding gene were 82% at the nucleotide sequence level and 87% at the amino acid sequence level in the regions to be translated into proteins. The nucleotide sequence of the chicken homologue is represented by SEQ ID NO: 29 and the amino acid sequence of the same is represented by SEQ ID NO: 30. In addition, the sequence identities of the human homologue-encoding genes and the chicken homologue-encoding gene were 81% to 82% at the nucleotide sequence level and 86% at the amino acid sequence level in the regions to be translated into proteins.

(4) Gene expression analysis in each tissue

[0126] The expression of genes obtained by the above method was examined in dog and human normal tissues and various cell lines by an RT-PCR method. Reverse transcription reaction was performed as follows. Specifically, total RNA was extracted from 50 mg to 100 mg of the tissue or 5 to 10 x 10⁶ cells of the cell line using a TRIZOL reagent (Invitrogen) according to the accompanying protocols. cDNA was synthesized with the total RNA using a Superscript First-Strand Synthesis System for RT-PCR (Invitrogen) according to the accompanying protocols. PCR was performed as follows using primers of SEQ ID NOS: 33 and 34 specific to the obtained genes. Specifically, reagents and an accompanying buffer were added to 0.25 µl of the sample prepared by the reverse transcription reaction to a total volume of 25 µl, so that the resultant contained the above primers of 2 µM each, dNTPs of 0.2 mM each, and 0.65 U ExTaq polymerase (Takara Shuzo Co., Ltd.). PCR was carried out by repeating a cycle of 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 30 seconds 30 times using a Thermal Cycler (BIO RAD). The above gene-specific primers are capable of amplifying the region ranging from nucleotides 206 to 632 in the nucleotide sequence of SEQ ID NO: 5 (dog CAPRIN-1 gene) and the region ranging from nucleotides 698 to 1124 in the nucleotide sequence of SEQ ID NO: 1 (human CAPRIN-1 gene). As a control for comparison, GAPDH-specific primers of SEQ ID NOS: 35 and 36 were also used concurrently. As a result, as shown in Fig. 1, strong expression was observed in testis among normal dog tissues, while expression was observed in dog breast cancer and adenocarcinoma tissues. Moreover, the observation of the expression of the human homologues from the obtained genes was also carried out. As a result, similarly to the case of the dog CAPRIN-1 gene, expression could be observed in only testis among normal tissues. However, in the case of cancer cells, expression was detected in many types of cancer cell lines, including breast cancer, brain tumor, leukemia, lung cancer, and esophageal cancer cell lines. Expression was observed particularly in many breast cancer cell lines. It was confirmed by the results that the expression of CAPRIN-1 is not observed in normal tissues other than testis, while CAPRIN-1 was expressed in many cancer cells and particularly in breast cancer cell lines.

[0127] In Fig. 1, reference number 1 on each vertical axis indicates the expression patterns of genes identified above and reference number 2 indicates the expression patterns of the GAPDH gene as a control.

(5) Immunohistochemical staining

(5)-1 CAPRIN-1 expression in mouse and dog normal tissues

[0128] Mice (Balb/c, female) and dogs (beagles, female) were exsanguinated under ether anesthesia and ketamine/isoflurane anesthesia. After laparotomy, each organ (stomach, liver, eyeball, thymus gland, muscle, bone marrow, uterus, small bowel, esophagus, heart, kidney, salivary gland, large bowel, mammary gland, brain, lung, skin, adrenal gland, ovary, pancreas, spleen, and bladder) was transferred to a 10-cm dish containing PBS. Each organ was cut open in PBS and then subjected to perfusion fixation overnight in 0.1 M phosphate buffer (pH 7.4) containing 4% paraformaldehyde (PFA). The perfusion solution was discarded, the tissue surface of each organ was rinsed with PBS, a PBS solution containing 10% sucrose was added to a 50-ml centrifuge tube, each tissue was added to the tube, and then the tube was shaken using a rotor at 4°C for 2 hours. The solution was replaced by a PBS solution containing 20% sucrose, and then left to stand at 4°C until the tissue sank. The solution was replaced by a PBS solution containing 30% sucrose and then left to stand at 4°C until the tissue sank. The tissue was removed and then needed portions were excised with a surgical scalpel. Next, an OCT compound (Tissue Tek) was added to the tissue so that it was thoroughly applied to the tissue surface, and then the tissue was placed in a cryomold. The cryomold was placed on dry ice for quick freezing. Thereafter, the tissue was sliced to 10 µm to 20 µm using a cryostat (LEICA). Slices were air-dried on slide glasses using a hair dryer for 30 minutes, to prepare the sliced tissue mounted on a slide glass. Next, each sample was placed in a staining bottle filled with PBS-T (saline containing 0.05% Tween20) and then subjected to replacement with PBS-T being repeated three times every 5 minutes. Excess water around the sections was removed with Kimwipes, and then the sections were circled using a DAKOPEN (DAKO). As blocking solutions, an MOM mouse Ig blocking reagent (VECTASTAIN) and a PBS-T solution containing 10% FBS were overlaid on mouse tissue and dog tissue, respectively, and then left to stand in a moist chamber at room temperature for 1 hour. Next, a solution of the anti-CAPRIN-1 monoclonal antibody (monoclonal antibody #1 prepared in Example 4) of 10 µg/ml adjusted with a blocking solution, which reacts with cancer cell surfaces and comprises the heavy chain variable region of SEQ ID NO: 42 and the light chain variable region of SEQ ID NO: 46, was placed on and then left to stand overnight in a moist chamber at 4°C. 10 minutes of washing with PBS-T was performed 3 times, and then an MOM biotin-labeled anti-IgG antibody (VECTASTAIN) diluted 250-fold with the blocking solution was placed and then left to stand at room temperature for 1 hour in a moist chamber. After ten (10) minutes of washing with PBS-T was performed 3 times, an avidin-biotin ABC reagent (VECTASTAIN) was placed on, and then the sample was left to stand in a moist chamber at room temperature for 5 minutes. After ten (10) minutes of washing with PBS-T was performed 3 times, a DAB coloring solution (DAB 10 mg + 30% H₂O₂ 10 µl/0.05 M Tris-HCl (pH 7.6) 50 ml) was placed on, and then the sample was left to stand in a moist chamber at room temperature

for 30 minutes. After rinsing with distilled water, a hematoxylin reagent (DAKO) was placed on, the sample was left to stand at room temperature for 1 minute, and then rinsed with distilled water. The slide glass was immersed in 70%, 80%, 90%, 95%, and then 100% ethanol solutions in such order for 1 minute each and then left to stand overnight in xylene. The slide glass was removed, sealed in Glycergel Mounting Medium (DAKO), and then observed. As a result, the expression of CAPRIN-1 was slightly observed within cells of each tissue of salivary gland, kidney, colon, and stomach, but the expression of the same was not observed on cell surfaces. Furthermore, no expression was observed in tissues from other organs.

(5)-2 CAPRIN-1 expression in dog breast cancer tissue

[0129] Frozen section slides were prepared by a method similar to the above using 108 frozen breast cancer tissue specimens of dogs pathologically diagnosed as having malignant breast cancer, and immunohistochemical staining was performed using the monoclonal antibody #1 prepared in Example 4. As a result, the expression of CAPRIN-1 was observed in 100 out of 108 specimens (92.5%) and CAPRIN-1 was strongly expressed on the surfaces of cancer cells with a particularly high grade of atypism.

(5)-3 CAPRIN-1 expression in human breast cancer tissues

[0130] Immunohistochemical staining was performed using 188 breast cancer tissue specimens on a paraffin-embedded human breast cancer tissue array (BIOMAX). After 3 hours of treatment of the human breast cancer tissue array at 60°C, the array was placed in a staining bottle filled with xylene, followed by xylene replacement being repeated three times every 5 minutes. Next, a similar procedure was performed with ethanol and PBS-T instead of xylene. The human breast cancer tissue array was placed in a staining bottle filled with 10 mM citrate buffer (pH 6.0) containing 0.05% Tween20. After 5 minutes of treatment at 125°C, the array was left to stand at room temperature for 40 minutes or more. Excess water around the sections was removed with Kimwipes, the sections were circled with a DAKOPEN, and Peroxidase Block (DAKO) was added dropwise in appropriate amounts. After left to stand at room temperature for 5 minutes, the array was placed in a staining bottle filled with PBS-T, followed by PBS-T replacement being repeated three times every 5 minutes. As a blocking solution, a PBS-T solution containing 10% FBS was placed on the array, and then the array was left to stand in a moist chamber at room temperature for 1 hour. Next, a solution of the monoclonal antibody #1 of 10 µg/ml adjusted with a PBS-T solution containing 5% FBS, which reacts with cancer cell surfaces and had been prepared in Example 4, was placed on, and the array was left to stand overnight in a moist chamber at 4°C. After ten (10) minutes of washing with PBS-T was performed 3 times, Peroxidase Labeled Polymer Conjugated (DAKO) was added dropwise in appropriate amounts and then the array was left to stand in a moist chamber at room temperature for 30 minutes. After ten (10) minutes of washing with PBS-T was performed 3 times, a DAB coloring solution (DAKO) was placed on and then it was left to stand at room temperature for about 10 minutes. The coloring solution was discarded, 10 minutes of washing with PBS-T was performed 3 times, and then it was rinsed with distilled water. The array was immersed in 70%, 80%, 90%, 95%, and then 100% ethanol solutions in such order for 1 minute each, and then left to stand in xylene overnight. The slide glass was removed, sealed in Glycergel Mounting Medium (DAKO), and then observed. As a result, the strong expression of CAPRIN-1 was observed in 138 out of a total of 188 breast cancer tissue specimens (73%).

(5)-4 CAPRIN-1 expression in human malignant brain tumor

[0131] Immunohistochemical staining was performed according to a method similar to that used in (5)-3 above with 247 malignant brain tumor tissue specimens on a paraffin-embedded human malignant brain tumor tissue array (BIOMAX), using the monoclonal antibody #1 prepared in Example 4. As a result, the strong expression of CAPRIN-1 was observed in 227 out of a total of 247 malignant brain tumor tissue specimens (92%).

(5)-5 CAPRIN-1 expression in human breast cancer metastasized lymph node

[0132] Immunohistochemical staining was performed according to a method similar to that in (5)-3 above with 150 breast cancer metastasized lymph node tissue specimens on a paraffin-embedded human breast cancer metastasized lymph node tissue array (BIOMAX), using the monoclonal antibody #1 prepared in Example 4. As a result, the strong expression of CAPRIN-1 was observed in 136 out of a total of 150 breast cancer metastasized lymph node tissue specimens (90%). Specifically, it was revealed that CAPRIN-1 was strongly expressed also in cancer tissues that had metastasized from breast cancer.

(5)-6 CAPRIN-1 expression in various human cancer tissues

[0133] Immunohistochemical staining was performed according to a method similar to the above with specimens on various paraffin-embedded human cancer tissue arrays (BIOMAX), using the monoclonal antibody #1 prepared in Example 4. As a result, the strong expression of CAPRIN-1 was observed in esophageal cancer, colon cancer, rectal cancer, lung cancer, renal cancer, bladder cancer, and uterine cervix cancer.

Example 2 Preparation of novel human cancer antigen protein

(1) Preparation of recombinant protein

[0134] Based on the gene of SEQ ID NO: 1 obtained in Example 1, a recombinant protein from the human homologous gene was prepared by the following method. PCR was performed in a total volume of 50 μ l with 1 μ l of cDNA, two primers (SEQ ID NOS: 37 and 38 comprising *Sac* I and *Xho* I restriction enzyme cleavage sequences) of 0.4 μ M each, 0.2 mM dNTP, and 1.25U PrimeSTAR HS polymerase (Takara Shuzo Co., Ltd.), prepared by adding the reagents and an accompanying buffer. The expression had been confirmed by an RT-PCR method for the cDNA used herein from among various tissue or cell-derived cDNAs prepared in Example 1. PCR was performed by repeating a cycle of 98°C for 10 seconds and 68°C for 2.5 minutes 30 times using a Thermal Cycler (BIO RAD). The above two primers are capable of amplifying a region encoding the entire amino acid sequence of SEQ ID NO: 2. After PCR, the thus amplified DNA was subjected to electrophoresis on 1% agarose gel, and then an about 2.1 kbp DNA fragment was purified using a QIAquick Gel Extraction Kit (QIAGEN).

[0135] The thus purified DNA fragment was ligated to a cloning vector PCR-Blunt (Invitrogen). After transformation of *Escherichia coli* with it, plasmid was collected. It was verified by sequencing that the thus amplified gene fragment has the sequence of interest. The plasmid having a matched sequence with the sequence of interest was treated with *Sac* I and *Xho* I restriction enzymes and then purified with a QIAquick Gel Extraction Kit. The gene sequence of interest was inserted into an *Escherichia coli* expression vector pET30a (Novagen) treated with *Sac* I and *Xho* I restriction enzymes. A His-tag fused recombinant protein can be produced using the vector. The plasmid was transformed into *Escherichia coli* for expression, BL21(DE3), and then expression was induced with 1 mM IPTG, so that the protein of interest was expressed in *Escherichia coli*.

(2) Purification of recombinant protein

[0136] The above-obtained recombinant *Escherichia coli* expressing the gene of SEQ ID NO: 1 was cultured in LB medium containing 30 μ g/ml kanamycin at 37°C until absorbance at 600 nm reached around 0.7, isopropyl- β -D-1-thiogalactopyranoside was added at a final concentration of 1 mM, and then cells were cultured at 37°C for 4 hours. Subsequently, centrifugation was performed at 4800 rpm for 10 minutes and then cells were collected. The resulting cell pellet was suspended in phosphate buffered saline and centrifuged at 4800 rpm for 10 minutes, and then cells were washed.

[0137] The cells were suspended in phosphate buffered saline and then disrupted by ultrasonication on ice. The resulting lysate of the ultrasonicated *Escherichia coli* was subjected to centrifugation at 6000 rpm for 20 minutes, and then the resulting supernatant was regarded as a soluble fraction and the precipitate was regarded as an insoluble fraction.

[0138] The soluble fraction was added to a nickel chelate column adjusted according to a conventional method (carrier: Chelating Sepharose™ Fast Flow (GE Healthcare); column capacity of 5 ml; and equilibration buffer: 50 mM hydrochloride buffer (pH 8.0)). Unadsorbed fractions were washed off with 50 mM hydrochloride buffer (pH 8.0) in an amount 10 times the column capacity and 20 mM phosphate buffer (pH 8.0) containing 20 mM imidazole. Immediately after washing, 6 beds were eluted with 20 mM phosphate buffer (pH 8.0) containing 100 mM imidazole. The elution of the protein of interest was confirmed by Coomassie staining on the elution fraction with 20 mM phosphate buffer (pH 8.0) containing 100 mM imidazole, and then the elution fraction was added to a strong anion exchange column (carrier: Q Sepharose™ Fast Flow (GE Healthcare); column capacity of 5 ml; and 20 mM phosphate buffer (pH 8.0) as an equilibration buffer). An unadsorbed fraction was washed off with 20 mM phosphate buffer (pH 7.0) in an amount 10 times the column capacity and 20 mM phosphate buffer (pH 7.0) containing 200 mM sodium chloride. Immediately after washing, 5 beds were eluted with 20 mM phosphate buffer (pH 7.0) containing 400 mM sodium chloride, and thus the purified fraction of the protein having the amino acid sequence represented by SEQ ID NO: 2 was obtained.

[0139] 200 μ l of each purified sample obtained by the above method was dispensed into 1 ml of reaction buffer (20 mM Tris-HCl, 50 mM, NaCl, 2 mM CaCl₂, pH 7.4), followed by addition of 2 μ l of enterokinase (Novagen). After that, the resultant was left to stand overnight at room temperature for reaction so that His-tag was cleaved off, and then purification was performed using an Enterokinase Cleavage Capture Kit (Novagen) according to the accompanying protocols. Next, 1.2 ml of the purified sample obtained by the above method was subjected to the buffer replacement with physiological

phosphate buffer (Nissui Pharmaceutical Co., Ltd.) using an ultrafiltration NANOSEP 10K OMEGA (PALL). Further, sterile filtration was performed using HT Tuffryn Acrodisc 0.22 μm (PALL) and then the resultant was used for the following experiment.

Example 3 Preparation of chicken monoclonal antibody against CAPRIN-1

[0140] 300 μg of the antigen protein (human CAPRIN-1) () shown by SEQ ID NO: 2 prepared in Example 2 was mixed with an equivalent amount of Freund's complete adjuvant, and then this was used as an antigen solution for one chicken. The antigen solution was intraperitoneally administered to 7-week-old chickens, and then the administration was performed 7 times every 4 weeks, and thus immunization was completed. Each spleen was excised on day 4 after the final immunization, and sandwiched between two sterilized slide glasses and then crushed. The resultant was washed with PBS(-) (Nissui) and then centrifuged at 1500 rpm for 10 minutes to remove the supernatant. This procedure was repeated 3 times, so that splenocytes were obtained. The thus obtained splenocytes and chicken myeloma cells deficient in light chain were mixed at a ratio of 5 : 1. The used chicken myeloma cells had been established from a chicken by a transformation using an avian reticuloendotheliosis virus. A PEG solution prepared by mixing 200 μl of IMDM medium containing 10% FBS heated at 37°C and 800 μl of PEG1500 (Boehringer) was added to the mixture, left to stand for 5 minutes for cell fusion, and then subjected to centrifugation at 1700 rpm for 5 minutes. After removal of the supernatant, cells were suspended in 300 ml of IMDM medium containing 10% FBS, supplemented with a HAT solution (Gibco) (2% equivalent) (HAT selective medium), and then the cell suspension was plated on thirty 96-well plates (Nunc) at 100 μl per well. Cells were cultured for 7 days at 37°C under conditions of 5% CO_2 , so that hybridoma prepared by fusion of splenocytes and chicken myeloma cells were obtained.

[0141] Hybridomas were selected using as a marker the binding affinity of the antibody produced by the prepared hybridomas to the CAPRIN-1 protein. The CAPRIN-1 protein solution (1 $\mu\text{g}/\text{ml}$) prepared in Example 2 was added to a 96-well plate at 100 μl per well and then left to stand at 4°C for 18 hours. Each well was washed 3 times with PBS-T, 400 μl of a 0.5% Bovine Serum Albumin (BSA) solution (Sigma) was added per well, and then the plate was left to stand at room temperature for 3 hours. The solution was removed, and then the wells were washed three times with 400 μl of PBS-T per well. The culture supernatant of the above-obtained hybridomas was added at 100 μl per well, and then left to stand at room temperature for 2 hours. After washing each well three times with PBS-T, an HRP-labeled anti-chicken IgY antibody (SIGMA) diluted 5000-fold with PBS was added at 100 μl per well and the resultant was then left to stand at room temperature for 1 hour. After washing the wells three times with PBS-T, 100 μl of a TMB substrate solution (Thermo) was added per well and then left to stand for 15 to 30 minutes for coloring reaction. After color development, 100 μl of 1N sulfuric acid was added per well to stop the reaction, and then absorbances at 450 nm and 595 nm were measured using an absorption spectrometer. As a result, several hybridomas producing antibodies with high absorbance values were selected.

[0142] The thus selected hybridomas were added to a 96-well plate at 0.5 cells per well and then cultured. After 1 week, hybridomas that had formed single colonies in wells were observed. These cells in the wells were further cultured, and then hybridomas were selected using as a marker the binding affinity of antibodies produced by the cloned hybridomas to the CAPRIN-1 protein. The CAPRIN-1 protein solution (1 $\mu\text{g}/\text{ml}$) prepared in Example 2 was added to a 96-well plate at 100 μl per well, and then left to stand at 4°C for 18 hours. Each well was washed with PBS-T three times, 400 μl of a 0.5% BSA solution was added per well, and then the resultant was left to stand at room temperature for 3 hours. The solution was removed, and then the wells were washed three times with 400 μl of PBS-T per well. 100 μl of each culture supernatant of the above-obtained hybridomas was added per well, and then the plate was left to stand at room temperature for 2 hours. After washing each well three times with PBS-T, 100 μl of an HRP-labeled anti-chicken IgY antibody (SIGMA) diluted 5000-fold with PBS was added per well and then left to stand at room temperature for 1 hour. After washing the wells three times with PBS-T, 100 μl of a TMB substrate solution (Thermo) was added per well, and then left to stand for 15 to 30 minutes for coloring reaction. After color development, 100 μl of 1N sulfuric acid was added per well to stop the reaction and then absorbances at 450 nm and 595 nm were measured using an absorption spectrometer. As a result, several hybridoma cell lines producing monoclonal antibodies reactive with the CAPRIN-1 protein were obtained.

[0143] Next, of those monoclonal antibodies, antibodies reactive with the cell surfaces of breast cancer cells expressing CAPRIN-1 were selected. Specifically, 5×10^5 cells of the human breast cancer cell line MDA-MB-231V were subjected to centrifugation in a 1.5-ml microcentrifuge tube, and 100 μl of the culture supernatant of each of the above hybridomas was added to the tube, and then the tube was left to stand on ice for 1 hour. After washing with PBS, an FITC-labeled goat anti-chicken IgG (H+L) antibody (SouthernBiotech) diluted 30-fold with PBS containing 0.1% FBS was added, and then the resultant was left to stand on ice for 1 hour. After washing with PBS, fluorescence intensity was measured using a FACS caliber (Becton, Dickinson and Company). Meanwhile, procedures similar to the above were performed for medium for culturing hybridomas, so that a control sample was obtained. As a result, one monoclonal antibody (monoclonal antibody #1) that had exhibited fluorescence intensity stronger than that of the control, and that is, that reacted

with the cell surfaces of CAPRIN-1-expressing breast cancer cells, was selected.

Example 4 Characterization of selected antibody

(1) Cloning of genes of anti-CAPRIN-1 monoclonal antibody variable regions

[0144] mRNA was extracted from a chicken-derived hybridoma cell line producing monoclonal antibodies (selected in Example 3) reactive with the surfaces of CAPRIN-1-expressing breast cancer cells. An RT-PCR method using primers specific to the chicken FR1-derived sequence and the chicken FR4-derived sequence was performed therefor, and the gene of the heavy chain variable (VH) region and the gene of the light chain variable (VL) region of the antibody were obtained. mRNA was also extracted from two mouse-derived hybridoma cell lines producing monoclonal antibodies reactive with the surfaces of CAPRIN-1-expressing breast cancer cells. An RT-PCR method using primers specific to the mouse FR1-derived sequence and the mouse FR4-derived sequence was performed therefor, and the gene of the heavy chain variable (VH) region and the gene of the light chain variable (VL) region of each antibody were obtained. For sequence determination, these genes were cloned into a pCR2.1 vector (Invitrogen).

(1)-1 RT-PCR

[0145] After extraction of total RNA from 10^6 cells of each hybridoma cell line using a High Pure RNA Isolation Kit (Roche), cDNA was synthesized using a PrimeScriptII 1st strand cDNA Synthesis Kit (Takara). These procedures were performed according to protocols attached to each kit.

[0146] The gene of the chicken antibody heavy chain variable region and the gene of the chicken antibody light chain variable region, and the gene of the mouse antibody heavy chain variable region and the gene of the mouse antibody light chain variable region were each amplified by a PCR method according to a conventional method using the thus synthesized cDNA as a template and KOD-Plus-DNA Polymerase (TOYOBO).

[0147] To obtain the gene of the chicken antibody VH region, a primer specific to the chicken heavy chain FR1 sequence and a primer specific to the chicken heavy chain FR4 sequence were used. Furthermore, to obtain the gene of the VL region, a primer specific to the chicken light chain FR1 sequence and a primer specific to the chicken light chain FR4 were used. The genes of mouse antibody VH and VL regions were obtained in a manner similar to the above. Specifically, a primer specific to the mouse heavy chain FR1 sequence, a primer specific to the mouse heavy chain FR4 sequence, a primer specific to the mouse light chain FR1 sequence, and a primer specific to the mouse light chain FR4 were used.

[0148] The thus obtained PCR products were each subjected to agarose gel electrophoresis, and DNA bands of the VH region and the VL region were excised. DNA fragments were purified using a QIAquick Gel purification kit (QIAGEN) according to the accompanying protocols. The purified DNA was cloned into a pCR2.1 vector using a TA cloning kit (Invitrogen). The ligated vector was transformed into DH5 competent cells (TOYOBO) according to a conventional method. 10 clones of each transformant were cultured overnight in medium (100 μ g/ml ampicillin) at 37°C, and then plasmid DNA was purified using a Qiaspin Miniprep kit (QIAGEN).

(1)-2 Sequence determination

[0149] The gene sequences of the VH region and the VL region in each plasmid obtained above were analyzed with an M13 forward primer (SEQ ID NO: 47) and an M13 reverse primer (SEQ ID NO: 48) on a fluorescence sequencer (DNA sequencer 3130XL; ABI), using a Big Dye Terminator Ver3.1 Cycle Sequencing Kit (ABI) according to the accompanying protocols. As a result, each gene sequence was determined. The sequences were identical among the 10 clones.

[0150] The thus obtained gene sequence encoding the heavy chain variable region of the chicken-derived monoclonal antibody is represented by SEQ ID NO: 49 and the amino acid sequence thereof is represented by SEQ ID NO: 42, and the thus obtained gene sequence encoding the light chain variable region is represented by SEQ ID NO: 50 and the amino acid sequence thereof is represented by SEQ ID NO: 46.

[0151] Specifically, it was revealed that the monoclonal antibody #1 comprises the heavy chain variable region of SEQ ID NO: 42 and the light chain variable region of SEQ ID NO: 46, wherein CDR1, CDR2, and CDR3 in the heavy chain variable region consist of the amino acid sequences of SEQ ID NOS: 39, 40, and 41, respectively, and the CDR1, CDR2, and CDR3 in the light chain variable region consist of the amino acid sequences of SEQ ID NOS: 43, 44, and 45, respectively.

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

[0152] An amplification fragment of the gene of the heavy chain variable region (SEQ ID NO: 42) of the chicken monoclonal antibody #1 obtained in (1) above was treated at both ends with restriction enzymes and then purified. The

resulting fragment was inserted into a pcDNA4/myc-His (Invitrogen) vector according to a conventional method, into which a chicken antibody-derived leader sequence comprising SEQ ID NO: 51 and a human IgG1 H-chain constant region comprising SEQ ID NO: 52 had already been inserted. Furthermore, an amplification fragment of the gene of the chicken monoclonal antibody #1 light chain variable region (SEQ ID NO: 46) was treated at both ends with restriction enzymes and then purified. The resulting fragment was inserted into a pcDNA3.1/myc-His (Invitrogen) vector according to a conventional method, into which a chicken antibody-derived leader sequence comprising SEQ ID NO: 51 and a human IgG1 L-chain constant region comprising SEQ ID NO: 53 had already been inserted.

[0153] Next, the above recombinant vector into which the heavy chain variable region (SEQ ID NO: 42) of the chicken monoclonal antibody #1 had been inserted, and the above recombinant vector into which the chicken monoclonal antibody #1 light chain variable region (SEQ ID NO: 46) had been inserted, were introduced into CHO-K1 cells (obtained from RIKEN Cell Bank). Specifically, 2×10^5 CHO-K1 cells cultured in 1 ml of Ham's F12 medium (Invitrogen) containing 10% FBS per well of a 12-well culture plate were washed with PBS(-). 1 ml of Ham's F12 medium containing 10% FBS was further added per well and then a mixture of 250 ng of each of the above vectors dissolved in 30 μ l of OptiMEM (Invitrogen) and 30 μ l of a Polyfect transfection reagent (QIAGEN) was added to each well. CHO-K1 cells into which the above recombinant vector had been introduced were cultured in Ham's F12 medium containing 10% FBS, supplemented with 200 μ g/ml Zeocin (Invitrogen) and 200 μ g/ml geneticin (Roche). CHO-K1 cells into which the above recombinant vector had been introduced were plated in a 96-well plate at 0.5 cells per well. Thus, a cell line stably producing a human-chicken chimeric antibody #1 (also referred to as #1) having the chicken monoclonal antibody #1 variable region was prepared. The thus prepared cell line was cultured in a 150 cm² flask containing 30 ml of serum-free OptiCHO medium (Invitrogen) at 5×10^5 cells/ml for 5 days. Then, a culture supernatant containing #1 was obtained.

[0154] With a method similar to the above, an amplification fragment of the gene of the heavy chain variable region (SEQ ID NO: 42) of the chicken monoclonal antibody #1 was treated at both ends with restriction enzymes and then purified. The resultant was inserted according to a conventional method into a pcDNA4/myc-His (Invitrogen) vector into which a chicken antibody-derived leader sequence and a mouse IgG1 H-chain constant region had already been inserted. Furthermore, an amplification fragment of the gene of the light chain variable region (SEQ ID NO: 46) of the chicken monoclonal antibody #1 was treated at both ends with restriction enzymes and then purified. The resultant was then inserted according to a conventional method into a pcDNA3.1/myc-His (Invitrogen) vector into which a chicken antibody-derived leader sequence and the mouse IgG1 L-chain constant region had already been inserted. The resultant was introduced into CHO-K1 cells in a manner similar to the above and thus a cell line stably producing a mouse-chicken chimeric antibody #1 comprising the chicken monoclonal antibody #1 variable region was prepared. The cells were cultured at 5×10^5 cells/ml using a 150cm² flask and 30 ml of serum free OptiCHO medium (Invitrogen) for 5 days, so that a culture supernatant containing the mouse-chicken chimeric antibody #1 was obtained.

(3) CAPRIN-1 expression on various cancer cell surfaces using anti-CAPRIN-1 antibody #1

[0155] Next, 7 breast cancer cell lines (MDA-MB-157, T47D, MRK-nu-1, MDA-MB-231V, BT20, SK-BR-3, and DA-MB-231T) for which CAPRIN-1 gene expression had been observed, and the other 3 breast cancer cell lines (MDA-MB-231C, MCF-7, and ZR75-1), 5 glioma cell lines (T98G, SNB19, U251, U87MG, and U373), 4 renal cancer cell lines (Caki-1, Caki-2, A498, and ACHN), 2 gastric cancer cell lines (MNK28 and MNK45), 5 colorectal cancer cell lines (HT29, LoVo, Caco2, SW480, and HCT116), 3 lung cancer cell lines (A549, QG56, and PC8), 4 leukemia cell lines (AML5, Namalwa, BDCM, RPI1788), one lymphoma cell line (Ramos), one uterine cervix cancer cell line (SW756), one bladder cancer cell line (T24), and one esophageal cancer cell line (KYSE180) were examined for CAPRIN-1 protein expression on the cell surfaces of each cell line using the culture supernatants of CHO-K1 cells containing #1 obtained in (2) above. 10^6 cells of each cell line were centrifuged in a 1.5 ml microcentrifuge tube. Each cell culture supernatant (100 μ l) of CHO-K1 cells containing #1 obtained in (2) above was added and then left to stand on ice for 1 hour. After washing with PBS, a FITC-labeled goat-anti human IgG (H+L) antibody (SouthernBiotech) and a FITC-labeled anti-mouse IgG (H+L) antibody (Invitrogen) diluted 500-fold with PBS containing 0.1% FBS were added and then left to stand on ice for 1 hour. After washing with PBS, fluorescence intensity was measured using a FACS Calibur (Becton, Dickinson and Company). Meanwhile, procedures similar to the above were performed using a culture supernatant of CHO-K1 cells into which no antibody gene had been introduced and medium for culturing hybridomas, so that a negative control sample was prepared. As a result, cells to which the antibody #1 had been added exhibited fluorescence intensity stronger by 20% or more than that of the control. Specifically, fluorescence intensity was enhanced to 4900% in the case of SK-BR-3 and 5000% in the case of MDA-MB-231V. It was revealed by these results that the CAPRIN-1 protein was expressed on the cell membrane surfaces of the above human cancer cell lines. The percentage of enhancement in the above fluorescence intensity was expressed as percentage of increase in mean fluorescence intensity (MFI level) in each type of cell and calculated by the following formula.

[0156] Percentage of increase in mean fluorescence intensity (percentage of enhancement in fluorescence intensity)(%) = ((MFI level in cells having reacted with anti-human CAPRIN-1 antibody) - (MFI level of the control)) / (MFI level

of control) x 100.

(4) Anti-tumor effects (ADCC activity) of anti-CAPRIN-1 antibody #1 against cancer cells

[0157] Next, the anti-CAPRIN-1 antibody #1 was evaluated for the cytotoxic activity (ADCC activity) against cancer cells. Each cell culture supernatant producing #1 obtained in (2) above was purified using Hitrap ProteinA Sepharose FF (GE HealthCare), subjected to buffer replacement with PBS(-), and then filtered with a 0.22 μ m filter (Millipore). The resultants were used as antibodies for activity measurement. 10^6 cells of MDA-MB-157 human breast cancer cell line were collected in a 50-ml centrifuge tube, 100 μ Ci chromium-51 was added, and then incubation was performed at 37°C for 2 hours. Subsequently, the resultant was washed three times with RPMI1640 medium containing 10% FBS. Cells were added to a 96-well V-bottom plate at 5×10^3 cells per well for use as target cells. The above purified antibodies were added to the cells at a final concentration of 1 μ g/ml. 2.5×10^5 cells of lymphocytes separated from human peripheral blood according to a conventional method were further added and then cultured for 4 hours at 37°C under conditions of 5% CO₂. After culture, the amount of chromium-51 released from damaged cancer cells in a culture supernatant was measured, and the ADCC activity of each anti-CAPRIN-1 antibody against cancer cells was calculated. As negative control samples, a sample prepared by adding PBS instead of the anti-CAPRIN-1 antibodies and a sample prepared by adding an isotype control antibody instead of anti-CAPRIN-1 antibodies were used. As a result, the antibody #1 exhibited 30% or more cytotoxic activity against MDA-MB-157 (see Fig. 2). In contrast, the activity in the sample prepared by adding PBS as a negative control and the activity in the sample prepared by adding the isotype control antibody as a negative control were 1.1% and 2.0%, respectively. Similarly, the antibody #1 was examined for the ADCC activity against other cancer cells including glioma cell lines T98G and U373, lung cancer cell lines A549 and QG56, renal cancer cell lines Caki-1 and ACHN, a uterine cervix cancer cell line SW756, a bladder cancer cell line T24, an esophageal cancer cell line KYSE180, gastric cancer cell lines MNK28 and MNK45, a colorectal cancer cell line SW480, a leukemia cell line AML5, and a lymphoma cell line Ramos. As a result, the anti-CAPRIN-1 antibody #1 exhibited 16.4% activity against T98G (1.2% in the case of the isotype control), 23.1% against U373 (3.2% in the case of the isotype control), 36.1% against A549 (3.0% in the case of the isotype control), 33.5% against QG56 (0.5% in the case of the isotype control), 28.3% against Caki-1 (2.6% in the case of the isotype control), 25.1% against ACHN (1.6% in the case of the isotype control), 27.9% against SW756 (2.2% in the case of the isotype control), 25.8% against T24 (2.0% in the case of the negative control), 26.7% against KYSE180 (3.0% in the case of the isotype control), 21.5% against MNK28 (1.9% in the case of the isotype control), 23.0% against MNK45 (3.0% in the case of the isotype control), 24.0% against SW480 (1.8% in the case of the isotype control), 8.3% against AML5 (1.8% in the case of the isotype control), and 8.0% against Ramos (2.2% in the case of the isotype control). It was demonstrated by the above results that the thus obtained anti-CAPRIN-1 antibody #1 damages various human cancer cells expressing CAPRIN-1.

(5) Anti-tumor effects (CDC activity) of anti-CAPRIN-1 antibody #1 against cancer cell

[0158] Next, anti-CAPRIN-1 antibody #1 was evaluated for its cytotoxic activity (CDC activity) against cancer cells. Blood collected from a rabbit was added to an Eppendorf tube, left to stand at room temperature for 60 minutes, and then subjected to 5 minutes of centrifugation at 3000 rpm. Thus, serum for measurement of CDC activity was prepared. 10^6 cells of human breast cancer cells MDA-MB-231V were collected in a 50-ml centrifuge tube, 100 μ Ci chromium-51 was added, and then incubation was performed at 37°C for 2 hours. The resultant was washed three times with RPMI medium containing 10% FBS. Subsequently, the cells were suspended in RPMI medium containing the above-prepared rabbit serum (50%), and then added to a 96-well V-bottom plate at 5×10^3 cells per well. The antibody #1 obtained in (5) above was added to the cells at a final concentration of 1 μ g/ml and then cells were cultured for 4 hours at 37°C under conditions of 5% CO₂. After culture, the amount of chromium-51 released from damaged tumor cells in a culture supernatant was measured, and then the CDC activity against MDA-MB-231 V was calculated. As a result, the antibody #1 exhibited 25% or more CDC activity. Therefore, it was revealed that #1 can damage cancer cells expressing CAPRIN-1 also by CDC activity.

Example 5 *In vivo* anti-tumor effects of anti-CAPRIN-1 antibody #1 in mice

[0159] Next, the thus obtained anti-CAPRIN-1 antibody #1 was evaluated for its *in vivo* anti-tumor effects in tumor-bearing mice. Antibodies used herein were prepared by column purification of the culture supernatant of each cell producing #1 in the same manner as described above.

[0160] The anti-tumor effects of the antibody #1 was examined using tumor-bearing mice into which a mouse-derived cancer cell line expressing CAPRIN-1 had been transplanted. 4T1 cells (purchased from ATCC) were transplanted subcutaneously to the dorsal region of 20 Balb/c mice (Japan SLC Inc.) at 5×10^5 cells/mouse. Cancers were allowed to grow to reach a size of about 5 mm in diameter. The antibody #1 was administered intraperitoneally to 10 tumor-

bearing mice from among the 20 mice in an amount of 200 μ g (in 200 μ l) for one mouse. Subsequently, the same amount of the antibody was administered intraperitoneally to each tumor-bearing mouse 3 times in total within 2 days. Cancer sizes were measured every day and anti-tumor effects were examined by observation. Meanwhile, as a control group, PBS (-) was administered instead of the antibodies to the remaining 10 tumor-bearing mice. As a result of the observation of the anti-tumor effects, in the test group to which the anti-CAPRIN-1 antibody #1 had been administered, cancers were found to have regressed to about 55% on day 4, about 32% on day 6, about 7% on day 8, and cancers were found to have almost completely regressed before days 10 to 14, when the tumor volume at the initiation of the antibody administration was designated 100% (see Fig. 3). In the control group to which PBS(-) had been administered, the tumor size was increased to about 170%, 270%, 440%, and 670% on days 4, 6, 8, and 11, respectively (see Fig. 3). It was demonstrated by the results that the obtained antibody #1 exhibits strong anti-tumor effects *in vivo* against cancer cells expressing CAPRIN-1. The tumor (cancer) size was calculated as a volume using the formula: length of major axis x length of minor axis x length of minor axis x 0.5.

Industrial Applicability

[0161] The antibodies of the present invention are useful for treating and/or preventing a cancer.

Sequence Listing Free Text

[0162] SEQ ID NOS: 31-38, 47, and 48: primers

SEQUENCE LISTING

[0163]

<110> Toray Industries, Inc.

<120> Pharmaceutical composition for treating and/or preventing cancer

<130> PH-4602-PCT

<150> JP 2010-023452

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25	tat gaa cat gcc tcc att cac ctg tgg gac ctg ctg gaa ggg aag gaa Tyr Glu His Ala Ser Ile His Leu Trp Asp Leu Leu Glu Gly Lys Glu 210 215 220	855
30	aaa cct gta tgt gga acc acc tat aaa gtt cta aag gaa att gtt gag Lys Pro Val Cys Gly Thr Thr Tyr Lys Val Leu Lys Glu Ile Val Glu 225 230 235	903
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75	cag ggt ccc tat aat ttc ata cag gat tca atg ctg gat ttt gaa aat Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe Glu Asn	1335

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					370					375					380																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
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	Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly	
	625 630 635	
5	tac cgc cct tca ttc tct aac act cca aac agt ggt tat aca cag tct Tyr Arg Pro Ser Phe Ser Asn Thr Pro Asn Ser Gly Tyr Thr Gln Ser	2151
	640 645 650	
10	cag ttc agt gct ccc cgg gat tac tct ggc tat caa cgg gat gga tat Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly Tyr Gln Arg Asp Gly Tyr	2199
	655 660 665 670	
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	675 680 685	
20	cca cga ggt cgt gga ggg ccc cca aga ccc aac aga ggg atg ccg caa Pro Arg Gly Arg Gly Gly Pro Pro Arg Pro Asn Arg Gly Met Pro Gln	2295
	690 695 700	
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	705	
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	1				5					10					15		
5	Pro	Pro	Pro	Pro	Ser	Gly	Ser	Ser	Gly	Ser	Glu	Ala	Ala	Ala	Gly	Ala	
				20					25					30			
	Gly	Ala	Ala	Ala	Pro	Ala	Ser	Gln	His	Pro	Ala	Thr	Gly	Thr	Gly	Ala	
10				35				40					45				
	Val	Gln	Thr	Glu	Ala	Met	Lys	Gln	Ile	Leu	Gly	Val	Ile	Asp	Lys	Lys	
		50					55					60					
15	Leu	Arg	Asn	Leu	Glu	Lys	Lys	Lys	Gly	Lys	Leu	Asp	Asp	Tyr	Gln	Glu	
	65					70					75					80	
	Arg	Met	Asn	Lys	Gly	Glu	Arg	Leu	Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	
20					85					90					95		
	Ser	Lys	Tyr	Gln	Glu	Val	Thr	Asn	Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	
25				100					105					110			
	Gln	Arg	Ser	Phe	Met	Ala	Leu	Ser	Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	
			115					120					125				
30	Lys	Thr	Ala	Arg	Arg	Glu	Gln	Leu	Met	Arg	Glu	Glu	Ala	Glu	Gln	Lys	
		130					135					140					
	Arg	Leu	Lys	Thr	Val	Leu	Glu	Leu	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	
35	145					150					155					160	
	Asp	Asp	Glu	Val	Arg	Thr	Asp	Leu	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	
40					165					170					175		
	Ile	Leu	Ser	Glu	Glu	Glu	Leu	Ser	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	
				180					185					190			
45	Val	Asp	Pro	Glu	Arg	Asp	Met	Ser	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	
			195					200					205				

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

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	450		455		460											
5	Asp	Gln	Ile	Gln	Ala	Thr	Ile	Ser	Leu	Asn	Thr	Asp	Gln	Thr	Thr	Ala
	465					470					475					480
	Ser	Ser	Ser	Leu	Pro	Ala	Ala	Ser	Gln	Pro	Gln	Val	Phe	Gln	Ala	Gly
10					485					490					495	
	Thr	Ser	Lys	Pro	Leu	His	Ser	Ser	Gly	Ile	Asn	Val	Asn	Ala	Ala	Pro
				500					505					510		
15	Phe	Gln	Ser	Met	Gln	Thr	Val	Phe	Asn	Met	Asn	Ala	Pro	Val	Pro	Pro
			515					520					525			
	Val	Asn	Glu	Pro	Glu	Thr	Leu	Lys	Gln	Gln	Asn	Gln	Tyr	Gln	Ala	Ser
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	Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp	
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35	Lys Thr Ala Arg Arg Glu Gln Leu Met Arg Glu Glu Ala Glu Gln Lys 130 135 140		
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	Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys	
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	Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Pro Ala Ala	
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	Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln	
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	His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln	
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	Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn	
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30	Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	Ser	Lys	Tyr	Gln	Glu	Val	Thr	Asn
				100					105					110		
35	Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg	Ser	Phe	Met	Ala	Leu	Ser
			115					120					125			
40	Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	Lys	Thr	Ala	Arg	Arg	Glu	Gln	Leu
45																
50																
55																

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	130					135						140				
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	145					150					155					160
10	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	Asp	Asp	Glu	Val	Arg	Thr	Asp	Leu
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15	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	Ile	Leu	Ser	Glu	Glu	Glu	Leu	Ser
				180					185					190		
20	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	Ala	Asp	Pro	Glu	Arg	Asp	Met	Ser
			195					200					205			
25	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	His	Ala	Ser	Ile	His	Leu	Trp	Asp
	210						215					220				
30	Leu	Leu	Glu	Gly	Lys	Glu	Lys	Ser	Val	Cys	Gly	Thr	Thr	Tyr	Lys	Ala
	225					230					235					240
35	Leu	Lys	Glu	Ile	Val	Glu	Arg	Val	Phe	Gln	Ser	Asn	Tyr	Phe	Asp	Ser
					245					250					255	
40	Thr	His	Asn	His	Gln	Asn	Gly	Leu	Cys	Glu	Glu	Glu	Glu	Ala	Ala	Ser
				260					265					270		
45	Ala	Pro	Thr	Val	Glu	Asp	Gln	Val	Ala	Glu	Ala	Glu	Pro	Glu	Pro	Ala
			275					280					285			
50	Glu	Glu	Tyr	Thr	Glu	Gln	Ser	Glu	Val	Glu	Ser	Thr	Glu	Tyr	Val	Asn
	290						295					300				
55	Arg	Gln	Phe	Met	Ala	Glu	Thr	Gln	Phe	Ser	Ser	Gly	Glu	Lys	Glu	Gln
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60	Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	Gln
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70	Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln
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	370						375					380				

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	Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	Val	Ser	Ser	Thr	Ser	Glu		435	440	445
15	Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	Pro	Ser	His	Ala	Thr	Glu		450	455	460
20	Gln	Arg	Pro	Gln	Lys	Glu	Pro	Ile	Asp	Gln	Ile	Gln	Ala	Thr	Ile	Ser		465	470	475
25	Leu	Asn	Thr	Asp	Gln	Thr	Thr	Ala	Ser	Ser	Ser	Leu	Pro	Ala	Ala	Ser		485	490	495
	Gln	Pro	Gln	Val	Phe	Gln	Ala	Gly	Thr	Ser	Lys	Pro	Leu	His	Ser	Ser		500	505	510
30	Gly	Ile	Asn	Val	Asn	Ala	Ala	Pro	Phe	Gln	Ser	Met	Gln	Thr	Val	Phe		515	520	525
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40	Gln	Gln	Asn	Gln	Tyr	Gln	Ala	Ser	Tyr	Asn	Gln	Ser	Phe	Ser	Ser	Gln		545	550	555
	Pro	His	Gln	Val	Glu	Gln	Thr	Asp	Leu	Gln	Gln	Glu	Gln	Leu	Gln	Thr		565	570	575
45	Val	Val	Gly	Thr	Tyr	His	Gly	Ser	Gln	Asp	Gln	Pro	His	Gln	Val	Thr		580	585	590
50	Gly	Asn	His	Gln	Gln	Pro	Pro	Gln	Gln	Asn	Thr	Gly	Phe	Pro	Arg	Ser		595	600	605
	Ser	Gln	Pro	Tyr	Tyr	Asn	Ser	Arg	Gly	Val	Ser	Arg	Gly	Gly	Ser	Arg		610	615	620
55	Gly	Ala	Arg	Gly	Leu	Met	Asn	Gly	Tyr	Arg	Gly	Pro	Ala	Asn	Gly	Phe		625	630	635
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	Arg	Gly	Gly	Tyr	Asp	Gly	Tyr	Arg	Pro	Ser	Phe	Ser	Asn	Thr	Pro	Asn
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5	Ser	Gly	Tyr	Thr	Gln	Ser	Gln	Phe	Ser	Ala	Pro	Arg	Asp	Tyr	Ser	Gly
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10	Tyr	Gln	Arg	Asp	Gly	Tyr	Gln	Gln	Asn	Phe	Lys	Arg	Gly	Ser	Gly	Gln
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5	ccg ccg ccc ccg tcg ggt tcc tcc ggg agc gag gcg gcg gcg gcg gcg	96
	Pro Pro Pro Pro Ser Gly Ser Ser Gly Ser Glu Ala Ala Ala Ala Ala	
	20 25 30	
10	ggg gcg gcg ggg gcg gcg ggg gcc ggg gcg gct gcg ccc gcc tcc cag	144
	Gly Ala Ala Gly Ala Ala Gly Ala Gly Ala Ala Ala Pro Ala Ser Gln	
	35 40 45	
15	cac ccc gcg acc ggc acc ggc gct gtc cag acc gag gcc atg aag cag	192
	His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln	
	50 55 60	
20	atc ctc ggg gtg atc gac aag aaa ctc cgg aac ctg gag aag aaa aag	240
	Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys	
	65 70 75 80	
25	ggc aag ctt gat gat tac cag gaa cga atg aac aaa ggg gaa agg ctt	288
	Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu	
	85 90 95	
30	aat caa gat cag ctg gat gcc gta tct aag tac cag gaa gtc aca aat	336
	Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn	
	100 105 110	
35	aac ttg gag ttt gca aaa gaa tta cag agg agt ttc atg gca tta agt	384
	Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu Ser	
	115 120 125	
40	caa gat att cag aaa aca ata aag aag act gca cgt cgg gag cag ctt	432
	Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln Leu	
	130 135 140	

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5	cag	tat	gtt	ttg	gac	aaa	ttg	gga	gat	gat	gaa	gtg	aga	act	gac	ctg	528
	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	Asp	Asp	Glu	Val	Arg	Thr	Asp	Leu	
					165					170					175		
10	aag	caa	ggt	ttg	aat	gga	gtg	cca	ata	ttg	tct	gaa	gaa	gaa	ttg	tcg	576
	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	Ile	Leu	Ser	Glu	Glu	Glu	Leu	Ser	
				180					185					190			
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	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	Ala	Asp	Pro	Glu	Arg	Asp	Met	Ser	
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	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	His	Ala	Ser	Ile	His	Leu	Trp	Asp	
	210					215					220						
25	ttg	ctg	gaa	gga	aag	gaa	aag	tct	gta	tgt	gga	aca	acc	tat	aaa	gca	720
	Leu	Leu	Glu	Gly	Lys	Glu	Lys	Ser	Val	Cys	Gly	Thr	Thr	Tyr	Lys	Ala	
	225				230					235						240	
30	cta	aag	gaa	att	gtt	gag	cgt	gtt	ttc	cag	tca	aat	tac	ttt	gac	agc	768
	Leu	Lys	Glu	Ile	Val	Glu	Arg	Val	Phe	Gln	Ser	Asn	Tyr	Phe	Asp	Ser	
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35	act	cac	aac	cac	cag	aat	ggg	cta	tgt	gag	gaa	gaa	gag	gca	gcc	tca	816
	Thr	His	Asn	His	Gln	Asn	Gly	Leu	Cys	Glu	Glu	Glu	Glu	Ala	Ala	Ser	
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	Ala	Pro	Thr	Val	Glu	Asp	Gln	Val	Ala	Glu	Ala	Glu	Pro	Glu	Pro	Ala	
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	Glu	Glu	Tyr	Thr	Glu	Gln	Ser	Glu	Val	Glu	Ser	Thr	Glu	Tyr	Val	Asn	
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	Arg	Gln	Phe	Met	Ala	Glu	Thr	Gln	Phe	Ser	Ser	Gly	Glu	Lys	Glu	Gln	
	305				310					315						320	
55	gta	gat	gag	tggt	acg	gtc	gaa	aca	gtg	gag	gtg	gtg	aat	tca	ctc	cag	1008
	Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	Gln	
				325					330						335		
60	cag	caa	cct	cag	gct	gcg	tct	cct	tca	gta	cca	gag	ccc	cac	tct	ttg	1056
	Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	Leu	
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65	act	ccg	gtg	gct	cag	gca	gat	ccc	ctt	gtg	aga	aga	cag	cga	gtc	cag	1104
	Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	Gln	
		355					360						365				
70	gac	ctt	atg	gcg	cag	atg	cag	ggg	ccc	tat	aat	ttc	ata	cag	gat	tca	1152
	Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Tyr	Asn	Phe	Ile	Gln	Asp	Ser	
	370				375							380					
75	atg	ctg	gat	ttt	gaa	aac	cag	aca	ctc	gat	cct	gcc	att	gta	tct	gca	1200
	Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	Pro	Ala	Ile	Val	Ser	Ala	

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	385		390		395		400	
5	cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc							1248
	Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys							
			405		410		415	
	cct cca gtt cat tct gaa tct aga ctt gct caa cct aat caa gtt cct							1296
	Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro							
			420		425		430	
10	gta caa cca gaa gct aca cag gtt cct ttg gtt tca tcc aca agt gag							1344
	Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu							
			435		440		445	
15	ggg tat aca gca tct caa ccc ttg tac cag cct tct cat gct aca gag							1392
	Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu							
			450		455		460	
	caa cga cca caa aag gaa cca att gac cag att cag gca aca atc tct							1440
	Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser							
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20	tta aat aca gac cag act aca gcg tca tca tcc ctt ccg gct gct tct							1488
	Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser							
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25	cag cct cag gta ttc cag gct ggg aca agc aaa cca tta cat agc agt							1536
	Gln Pro Gln Val Phe Gln Ala Gly Thr Ser Lys Pro Leu His Ser Ser							
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	gga atc aat gta aat gca gct cca ttc caa tcc atg caa acg gtg ttc							1584
	Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe							
			515		520		525	
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	Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu Lys							
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35	caa caa aat cag tac cag gcc agt tat aac cag agc ttt tct agt cag							1680
	Gln Gln Asn Gln Tyr Gln Ala Ser Tyr Asn Gln Ser Phe Ser Ser Gln							
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	cct cac caa gta gaa caa aca gac ctt cag caa gaa cag ctt caa aca							1728
	Pro His Gln Val Glu Gln Thr Asp Leu Gln Gln Glu Gln Leu Gln Thr							
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	gtg gtt ggc act tac cat ggt tcc cag gac cag ccc cac caa gtg act							1776
	Val Val Gly Thr Tyr His Gly Ser Gln Asp Gln Pro His Gln Val Thr							
			580		585		590	
45	ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc							1824
	Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser							
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50	agt cag ccc tat tac aat agt cgt ggt gtg tct cgt ggt ggt tcc cgt							1872
	Ser Gln Pro Tyr Tyr Asn Ser Arg Gly Val Ser Arg Gly Gly Ser Arg							
			610		615		620	
	ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc							1920
	Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe							
			625		630		635	
55	aga gga gga tat gat ggt tac cgc cct tca ttc tct aac act cca aac							1968

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	Ser	Gly	Tyr	Thr	Gln	Ser	Gln	Phe	Ser	Ala	Pro	Arg	Asp	Tyr	Ser	Gly	
				660					665					670			
	tat	cag	cgg	gga	tgc	cgc	aaa	tga	acactcagca	agtgaattaa	tctgattcac						2070
10	Tyr	Gln	Arg	Gly	Cys	Arg	Lys										
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25

30

35

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45

50

55

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	Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	Ser	Lys	Tyr	Gln	Glu	Val	Thr	Asn	
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	130						135					140					
30	Met	Arg	Glu	Glu	Ala	Glu	Gln	Lys	Arg	Leu	Lys	Thr	Val	Leu	Glu	Leu	
	145					150					155					160	
	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	Asp	Asp	Glu	Val	Arg	Thr	Asp	Leu	
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	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	Ile	Leu	Ser	Glu	Glu	Glu	Leu	Ser	
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40	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	Ala	Asp	Pro	Glu	Arg	Asp	Met	Ser	
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	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	His	Ala	Ser	Ile	His	Leu	Trp	Asp	
45		210					215					220					
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10	Glu Glu Tyr Thr Glu Gln Ser Glu Val Glu Ser Thr Glu Tyr Val Asn 290 295 300		
15	Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln 305 310 315 320		
20	Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln 325 330 335		
25	Gln Gln Pro Gln Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu 340 345 350		
30	Thr Pro Val Ala Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln 355 360 365		
35	Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser 370 375 380		
40	Met Leu Asp Phe Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala 385 390 395 400		
45	Gln Pro Met Asn Pro Thr Gln Asn Met Asp Met Pro Gln Leu Val Cys 405 410 415		
50	Pro Pro Val His Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Pro 420 425 430		
55	Val Gln Pro Glu Ala Thr Gln Val Pro Leu Val Ser Ser Thr Ser Glu 435 440 445		
	Gly Tyr Thr Ala Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Glu 450 455 460		
	Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser 465 470 475 480		
	Leu Asn Thr Asp Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser 485 490 495		
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	35 40 45	
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	His Pro Ala Thr Gly Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln	
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	Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys Lys	
	65 70 75 80	
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	Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg Leu	
	85 90 95	
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	Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr Asn	
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35		cag cct atg aat ccg aca caa aac atg gac atg ccc cag ctg gtt tgc	1248
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		Gln Arg Pro Gln Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser	
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		485 490 495	
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		Gly Ile Asn Val Asn Ala Ala Pro Phe Gln Ser Met Gln Thr Val Phe	
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20	ggt aac cat cag cag cct ccc cag cag aac act gga ttt cca cgt agc Gly Asn His Gln Gln Pro Pro Gln Gln Asn Thr Gly Phe Pro Arg Ser 595 600 605	1824		
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30	ggt gct aga ggc tta atg aat gga tac agg ggc cct gcc aat gga ttc Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg Gly Pro Ala Asn Gly Phe 625 630 635 640	1920		
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40	agt ggt tat aca cag tct cag ttc agt gct ccc cgg gac tac tct ggc Ser Gly Tyr Thr Gln Ser Gln Phe Ser Ala Pro Arg Asp Tyr Ser Gly 660 665 670	2016		
45	tat cag cgg gat gga tat cag cag aat ttc aag cga ggc tct ggg cag Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly Gln 675 680 685	2064		
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	65					70					75					80	
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	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	Ile	Leu	Ser	Glu	Glu	Glu	Leu	Ser	
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40	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	Ala	Asp	Pro	Glu	Arg	Asp	Met	Ser	
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	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	His	Ala	Ser	Ile	His	Leu	Trp	Asp	
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15	Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	Leu	
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10	Gln Gln Asn Gln Tyr	545	Gln Ala Ser Tyr Asn	550	Gln Ser Phe Ser Ser Gln
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15	Pro His Gln Val	565	Gln Thr Asp Leu	570	Gln Glu Gln Leu Gln Thr
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20	Val Val Gly Thr Tyr His	580	Gly Ser Gln Asp	585	Gln Pro His Gln Val Thr
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25	Gly Asn His Gln Gln Pro	595	Pro Gln Gln Asn Thr	600	Gly Phe Pro Arg Ser
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30	Ser Gln Pro Tyr Tyr Asn	610	Ser Arg Gly Val	615	Ser Arg Gly Gly Ser Arg
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35	Gly Ala Arg Gly Leu Met	625	Asn Gly Tyr Arg	630	Gly Pro Ala Asn Gly Phe
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45	Ser Gly Tyr Thr Gln Ser	660	Gln Phe Ser Ala Pro	665	Arg Asp Tyr Ser Gly
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	Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala Ser Ala Pro Thr Val							
			255			260		265
	gaa gac cag gca gct gaa gct gaa cct gag cca gtg gaa gaa tat act							927
	Glu Asp Gln Ala Ala Glu Ala Glu Pro Glu Pro Val Glu Glu Tyr Thr							
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	Glu Gln Asn Glu Val Glu Ser Thr Glu Tyr Val Asn Arg Gln Phe Met							
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	Ala Glu Thr Gln Phe Ser Ser Gly Glu Lys Glu Gln Val Asp Asp Trp							
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	Thr Val Glu Thr Val Glu Val Val Asn Ser Leu Gln Gln Gln Pro Gln							
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	Ala Ala Ser Pro Ser Val Pro Glu Pro His Ser Leu Thr Pro Val Ala							
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	Gln Ala Asp Pro Leu Val Arg Arg Gln Arg Val Gln Asp Leu Met Ala							
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	Gln Met Gln Gly Pro Tyr Asn Phe Ile Gln Asp Ser Met Leu Asp Phe							
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	gaa aac cag aca ctt gat cct gcc att gta tct gca cag ccg atg aat							1263
	Glu Asn Gln Thr Leu Asp Pro Ala Ile Val Ser Ala Gln Pro Met Asn							
			380			385		390
35	cca gca cag aac atg gac ata ccc cag ctg gtt tgc cct cca gtt cat							1311
	Pro Ala Gln Asn Met Asp Ile Pro Gln Leu Val Cys Pro Pro Val His							
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								410
40	tct gaa tct aga ctt gct caa cct aat caa gtt tct gta cag cca gaa							1359
	Ser Glu Ser Arg Leu Ala Gln Pro Asn Gln Val Ser Val Gln Pro Glu							
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	gct aca cag gtt cct ttg gtt tca tcc aca agt gag gga tat aca gca							1407
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	Ser Gln Pro Leu Tyr Gln Pro Ser His Ala Thr Asp Gln Arg Pro Gln							
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	Lys Glu Pro Ile Asp Gln Ile Gln Ala Thr Ile Ser Leu Asn Thr Asp							
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	Gln Thr Thr Ala Ser Ser Ser Leu Pro Ala Ala Ser Gln Pro Gln Val							
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55								490
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	Phe	Gln	Ala	Gly	Thr	Ser	Lys	Pro	Leu	His	Ser	Ser	Gly	Ile	Asn	Val	
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	Asn	Ala	Ala	Pro	Phe	Gln	Ser	Met	Gln	Thr	Val	Phe	Asn	Met	Asn	Ala	
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	Tyr	Gln	Ala	Ser	Tyr	Asn	Gln	Ser	Phe	Ser	Ser	Gln	Pro	His	Gln	Val	
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15	gaa	caa	aca	gag	ctt	cag	caa	gaa	cag	ctt	caa	aca	gtg	gtt	ggc	act	1791
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	Tyr	His	Gly	Ser	Gln	Asp	Gln	Pro	His	Gln	Val	Thr	Gly	Asn	His	Gln	
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	Gln	Pro	Pro	Gln	Gln	Asn	Thr	Gly	Phe	Pro	Arg	Ser	Asn	Gln	Pro	Tyr	
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	Thr	Gln	Ser	Gln	Phe	Ser	Ala	Pro	Arg	Asp	Tyr	Ser	Gly	Tyr	Gln	Arg	
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	gat	gga	tat	cag	cag	aat	ttc	aag	cga	ggc	tct	ggg	cag	agt	gga	cca	2127
	Asp	Gly	Tyr	Gln	Gln	Asn	Phe	Lys	Arg	Gly	Ser	Gly	Gln	Ser	Gly	Pro	
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	Arg	Gly	Ala	Pro	Arg	Gly	Arg	Gly	Gly	Pro	Pro	Arg	Pro	Asn	Arg	Gly	
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 Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg
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 Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met
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				100					105					110			
5	Ser	Phe	Met	Ala	Leu	Ser	Gln	Asp	Ile	Gln	Lys	Thr	Ile	Lys	Lys	Thr	
			115					120					125				
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10		130					135					140					
	Lys	Thr	Val	Leu	Glu	Leu	Gln	Tyr	Val	Leu	Asp	Lys	Leu	Gly	Asp	Asp	
	145					150					155					160	
15	Glu	Val	Arg	Thr	Asp	Leu	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	Ile	Leu	
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20				180					185						190		
	Pro	Glu	Arg	Asp	Met	Ser	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	His	Ala	
25			195					200					205				
	Ser	Ile	His	Leu	Trp	Asp	Leu	Leu	Glu	Gly	Lys	Glu	Lys	Pro	Val	Cys	
	210						215					220					
30	Gly	Thr	Thr	Tyr	Lys	Ala	Leu	Lys	Glu	Ile	Val	Glu	Arg	Val	Phe	Gln	
	225					230					235					240	
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35				245					250						255		
	Glu	Glu	Glu	Ala	Ala	Ser	Ala	Pro	Thr	Val	Glu	Asp	Gln	Ala	Ala	Glu	
				260					265					270			
40	Ala	Glu	Pro	Glu	Pro	Val	Glu	Glu	Tyr	Thr	Glu	Gln	Asn	Glu	Val	Glu	
			275					280					285				
	Ser	Thr	Glu	Tyr	Val	Asn	Arg	Gln	Phe	Met	Ala	Glu	Thr	Gln	Phe	Ser	
45		290					295					300					
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55	Pro	Glu	Pro	His	Ser	Leu	Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	
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5	Asn	Phe	Ile	Gln	Asp	Ser	Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	
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10	385					390					395					400	
	Ile	Pro	Gln	Leu	Val	Cys	Pro	Pro	Val	His	Ser	Glu	Ser	Arg	Leu	Ala	
					405					410					415		
15	Gln	Pro	Asn	Gln	Val	Ser	Val	Gln	Pro	Glu	Ala	Thr	Gln	Val	Pro	Leu	
				420					425					430			
	Val	Ser	Ser	Thr	Ser	Glu	Gly	Tyr	Thr	Ala	Ser	Gln	Pro	Leu	Tyr	Gln	
20			435					440					445				
	Pro	Ser	His	Ala	Thr	Asp	Gln	Arg	Pro	Gln	Lys	Glu	Pro	Ile	Asp	Gln	
25		450					455					460					
	Ile	Gln	Ala	Thr	Ile	Ser	Leu	Asn	Thr	Asp	Gln	Thr	Thr	Ala	Ser	Ser	
	465					470					475					480	
30	Ser	Leu	Pro	Ala	Ala	Ser	Gln	Pro	Gln	Val	Phe	Gln	Ala	Gly	Thr	Ser	
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	Lys	Pro	Leu	His	Ser	Ser	Gly	Ile	Asn	Val	Asn	Ala	Ala	Pro	Phe	Gln	
35				500					505					510			
	Ser	Met	Gln	Thr	Val	Phe	Asn	Met	Asn	Ala	Pro	Val	Pro	Pro	Val	Asn	
40			515					520					525				
	Glu	Pro	Glu	Thr	Leu	Lys	Gln	Gln	Asn	Gln	Tyr	Gln	Ala	Ser	Tyr	Asn	
		530					535					540					
45	Gln	Ser	Phe	Ser	Ser	Gln	Pro	His	Gln	Val	Glu	Gln	Thr	Glu	Leu	Gln	
	545					550					555					560	
	Gln	Glu	Gln	Leu	Gln	Thr	Val	Val	Gly	Thr	Tyr	His	Gly	Ser	Gln	Asp	
50					565					570					575		
	Gln	Pro	His	Gln	Val	Thr	Gly	Asn	His	Gln	Gln	Pro	Pro	Gln	Gln	Asn	
				580					585					590			
55	Thr	Gly	Phe	Pro	Arg	Ser	Asn	Gln	Pro	Tyr	Tyr	Asn	Ser	Arg	Gly	Val	

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5	Ser Arg Gly Gly Ser Arg Gly Ala Arg Gly Leu Met Asn Gly Tyr Arg 610 615 620			
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5	agg ctt aat cag gat cag ctg gat gct gtg tct aag tac cag gaa gtc	96
	Arg Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val	
	20 25 30	
10	aca aat aac ttg gag ttt gcg aaa gaa ttg cag agg agt ttc atg gcg	144
	Thr Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala	
	35 40 45	
15	ttg agt cag gat att cag aaa aca ata aag aag acg gca cgt cgg gag	192
	Leu Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu	
	50 55 60	
20	cag ctt atg aga gaa gaa gct gaa cag aaa cgt tta aaa act gta ctt	240
	Gln Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu	
	65 70 75 80	
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				85						90					95		
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	Asp	Leu	Lys	Gln	Gly	Leu	Asn	Gly	Val	Pro	Ile	Leu	Ser	Glu	Glu	Glu	
			100					105					110				
10	ttg	tcg	ctg	ttg	gat	gag	ttc	tac	aag	tta	gca	gac	cct	gta	cgg	gac	384
	Leu	Ser	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	Ala	Asp	Pro	Val	Arg	Asp	
			115				120						125				
15	atg	agc	ttg	agg	ttg	aat	gag	cag	tat	gag	cat	gcc	tcc	att	cac	ctg	432
	Met	Ser	Leu	Arg	Leu	Asn	Glu	Gln	Tyr	Glu	His	Ala	Ser	Ile	His	Leu	
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	Trp	Asp	Leu	Leu	Glu	Gly	Lys	Glu	Lys	Ser	Val	Cys	Gly	Thr	Thr	Tyr	
			145			150				155						160	
25	aaa	gct	ctg	agg	gaa	att	gtt	gag	cgt	gtt	ttc	cag	tcc	aac	tac	ttt	528
	Lys	Ala	Leu	Arg	Glu	Ile	Val	Glu	Arg	Val	Phe	Gln	Ser	Asn	Tyr	Phe	
				165					170						175		
30	gac	agc	acc	cac	aac	cac	cag	aat	ggg	ctc	tgt	gag	gag	gaa	gag	gct	576
	Asp	Ser	Thr	His	Asn	His	Gln	Asn	Gly	Leu	Cys	Glu	Glu	Glu	Glu	Ala	
				180					185					190			
35	acc	tca	gct	cca	aca	gct	gaa	gac	cag	gga	gct	gaa	gct	gaa	cct	gag	624
	Thr	Ser	Ala	Pro	Thr	Ala	Glu	Asp	Gln	Gly	Ala	Glu	Ala	Glu	Pro	Glu	
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	Pro	Ala	Glu	Glu	Tyr	Thr	Glu	Gln	Ser	Glu	Val	Glu	Ser	Thr	Glu	Tyr	
			210				215						220				
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	Gln	Val	Asp	Glu	Trp	Thr	Val	Glu	Thr	Val	Glu	Val	Val	Asn	Ser	Leu	
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	Gln	Gln	Gln	Pro	Gln	Ala	Ala	Ser	Pro	Ser	Val	Pro	Glu	Pro	His	Ser	
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	Leu	Thr	Pro	Val	Ala	Gln	Ala	Asp	Pro	Leu	Val	Arg	Arg	Gln	Arg	Val	
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	Gln	Asp	Leu	Met	Ala	Gln	Met	Gln	Gly	Pro	Tyr	Asn	Phe	Ile	Gln	Asp	
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70	tca	atg	ctg	gat	ttt	gaa	aac	cag	aca	ctt	gat	cct	gcc	att	gta	tct	960
	Ser	Met	Leu	Asp	Phe	Glu	Asn	Gln	Thr	Leu	Asp	Pro	Ala	Ile	Val	Ser	
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	Ala	Gln	Pro	Met	Asn	Pro	Ala	Gln	Asn	Met	Asp	Met	Pro	Gln	Leu	Val	
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	Glu Gln Arg Pro Gln Lys Glu Pro Thr Asp Gln Ile Gln Ala Thr Ile	
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25	tct cag cct cag gtg ttc cag gct ggg aca agc aaa cct tta cac agc	1296
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35	ttc aac atg aat gcc ccg gtt cct cct gtt aat gaa cca gaa act tta	1392
	Phe Asn Met Asn Ala Pro Val Pro Pro Val Asn Glu Pro Glu Thr Leu	
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15																
20																
25																
30																
35																
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45																
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55																

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	Gly Pro Ala Asn Gly Phe Arg Gly Gly Tyr Asp Gly Tyr Arg Pro Ser	
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 Asn Leu Glu Lys Lys Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met
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30	Ser	Glu	Glu	Glu	Leu	Ser	Leu	Leu	Asp	Glu	Phe	Tyr	Lys	Leu	Val	Asp	
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	acc ggc gcc gtc cag acc gag gcc atg aag cag att ctc ggc gta atc Thr Gly Ala Val Gln Thr Glu Ala Met Lys Gln Ile Leu Gly Val Ile 45 50 55	315
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10	Ala	Ala	Pro	Ala	Ser	Gln	His	Pro	Ala	Thr	Gly	Thr	Gly	Ala	Val	Gln
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25	Asn	Lys	Gly	Glu	Arg	Leu	Asn	Gln	Asp	Gln	Leu	Asp	Ala	Val	Ser	Lys
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30	Tyr	Gln	Glu	Val	Thr	Asn	Asn	Leu	Glu	Phe	Ala	Lys	Glu	Leu	Gln	Arg
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20 Lys Pro Leu His Ser Ser Gly Ile Asn Val Asn Ala Ala Pro Phe Gln
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Glu Pro Glu Thr Leu Lys Gln Gln Ser Gln Tyr Gln Ala Thr Tyr Asn
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30 Gln Ser Phe Ser Ser Gln Pro His Gln Val Glu Gln Thr Glu Leu Gln
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Gln Pro His Gln Val Pro Gly Asn His Gln Gln Pro Pro Gln Gln Asn
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	Gly Pro Gly Gly Asn Glu Gln Ala Pro Ala Ala Ala Ala Ala Pro	
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	Gln Ala Ser Gly Gly Ser Ile Thr Ser Val Gln Thr Glu Ala Met Lys	
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	Gln Ile Leu Gly Val Ile Asp Lys Lys Leu Arg Asn Leu Glu Lys Lys	
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	Lys Ser Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg	
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	Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr	
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	Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln	
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	Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu	
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	Leu Lys Gln Gly Ser Asn Gly Val Pro Val Leu Thr Glu Glu Glu Leu	
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	Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys	
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	Ala Leu Lys Glu Val Val Glu Arg Ile Leu Gln Thr Ser Tyr Phe Asp	
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	Ser Thr His Asn His Gln Asn Gly Leu Cys Glu Glu Glu Glu Ala Ala	
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	Pro Thr Pro Ala Val Glu Asp Thr Val Ala Glu Ala Glu Pro Asp Pro	
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	Ala Glu Glu Phe Thr Glu Pro Thr Glu Val Glu Ser Thr Glu Tyr Val	
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	Asn Arg Gln Phe Met Ala Glu Thr Gln Phe Ser Ser Ser Glu Lys Glu	
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	Gln Val Asp Glu Trp Thr Val Glu Thr Val Glu Val Val Asn Ser Leu	
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	Gln Asp Leu Met Ala Gln Met Gln Gly Pro Tyr Asn Phe Met Gln Asp	
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	aac tac cag cgg gat gga tat cag cag aac ttc aaa cgt ggt tct gga Asn Tyr Gln Arg Asp Gly Tyr Gln Gln Asn Phe Lys Arg Gly Ser Gly 660 665 670	2016		
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35	Lys	Ser	Lys	Leu	Asp	Asp	Tyr	Gln	Glu	Arg	Met	Asn	Lys	Gly	Glu	Arg	
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Claims

- 30 1. An antibody or a fragment thereof, which comprises a heavy chain variable region comprising CDRs 1 to 3 represented by SEQ ID NOS: 39, 40, and 41 respectively and a light chain variable region comprising CDRs 1 to 3 represented by SEQ ID NOS: 43, 44, and 45 respectively, and has immunological reactivity with a CAPRIN-1 protein.
- 35 2. The antibody or fragment thereof according to claim 1, which is a human antibody, humanized antibody, chimeric antibody, single chain antibody, or bispecific antibody.
3. A pharmaceutical composition comprising the antibody or fragment thereof of claim 1 or claim 2 as an active ingredient.
- 40 4. The pharmaceutical composition of claim 3, further comprising an antitumor agent.
5. A pharmaceutical combination, comprising the pharmaceutical composition of claim 3 and a pharmaceutical composition containing an antitumor agent.
- 45 6. The antibody or fragment thereof of claim 1 or claim 2, the pharmaceutical composition of claim 3 or claim 4 or the pharmaceutical combination of claim 5, for use as a medicament.
7. The antibody or fragment thereof of claim 1 or claim 2, the pharmaceutical composition of claim 3 or claim 4 or the pharmaceutical combination of claim 5, for use in a method for treating and/or preventing a cancer.
- 50 8. The antibody, fragment or pharmaceutical composition for use according to claim 7, wherein the method comprises administering to a subject the antibody or fragment thereof of claim 1 or claim 2 or the pharmaceutical composition of claim 3 and an antitumor agent.
- 55 9. An antitumor agent for use in a method for treating and/or preventing a cancer, wherein the method comprises administering to a subject the antitumor agent and an antibody or fragment thereof according to claim 1 or claim 2 or the pharmaceutical composition of claim 3.

10. The antibody, fragment, pharmaceutical composition, pharmaceutical combination or antitumor agent for use according to any one of claims 7 to 9, wherein the cancer is breast cancer, brain tumor, leukemia, lymphoma, lung cancer, mastocytoma, renal cancer, uterine cervix cancer, bladder cancer, esophageal cancer, gastric cancer, or colorectal cancer.

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Patentansprüche

1. Antikörper oder Fragment davon, der/das eine variable Schwerkettenregion, die die durch die Seq.-ID Nr. 39, 40 bzw. 41 dargestellten CDR 1 bis 3 umfasst, und eine variable Leichtkettenregion umfasst, die die durch die Seq.-ID Nr. 43, 44 bzw. 45 dargestellten CDR 1 bis 3 umfasst, und immunologische Reaktivität mit einem CAPRIN-1-Protein aufweist.
2. Antikörper oder Fragment davon nach Anspruch 1, wobei es sich um einen menschlichen Antikörper, einen humanisierten Antikörper, einen chimären Antikörper, einen einkettigen Antikörper oder einen bispezifischen Antikörper handelt.
3. Pharmazeutische Zusammensetzung, die einen Antikörper oder ein Fragment davon nach Anspruch 1 oder Anspruch 2 als aktiven Bestandteil umfasst.
4. Pharmazeutische Zusammensetzung nach Anspruch 3, die des Weiteren ein Antitumormittel umfasst.
5. Pharmazeutische Kombination, die eine pharmazeutische Zusammensetzung nach Anspruch 3 und eine ein Antitumormittel enthaltende pharmazeutische Zusammensetzung umfasst.
6. Antikörper oder Fragment davon nach Anspruch 1 oder Anspruch 2, pharmazeutische Zusammensetzung nach Anspruch 3 oder Anspruch 4 oder pharmazeutische Kombination nach Anspruch 5 zur Verwendung als Medikament.
7. Antikörper oder Fragment davon nach Anspruch 1 oder Anspruch 2, pharmazeutische Zusammensetzung nach Anspruch 3 oder Anspruch 4 oder pharmazeutische Kombination nach Anspruch 5 zur Verwendung in einem Verfahren zur Behandlung und/oder Prävention von Krebs.
8. Antikörper, Fragment oder pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 7, worin das Verfahren das Verabreichen eines Antikörpers oder eines Fragments davon nach Anspruch 1 oder 2 oder einer pharmazeutischen Zusammensetzung nach Anspruch 3 und eines Antitumormittels an ein Individuum umfasst.
9. Antitumormittel zur Verwendung in einem Verfahren zur Behandlung und/oder Prävention von Krebs, worin das Verfahren das Verabreichen des Antitumormittels und eines Antikörpers oder eines Fragments davon nach Anspruch 1 oder 2 oder einer pharmazeutischen Zusammensetzung nach Anspruch 3 an ein Individuum umfasst.
10. Antikörper, Fragment, pharmazeutische Zusammensetzung, pharmazeutische Kombination oder Antitumormittel zur Verwendung nach einem der Ansprüche 7 bis 9, worin der Krebs Brustkrebs, ein Gehirntumor, Leukämie, ein Lymphom, Lungenkrebs, ein Mastozytom, Nierenkrebs, Gebärmutterhalskrebs, Blasenkrebs, Speiseröhrenkrebs, Magenkrebs oder Kolorektalkrebs ist.

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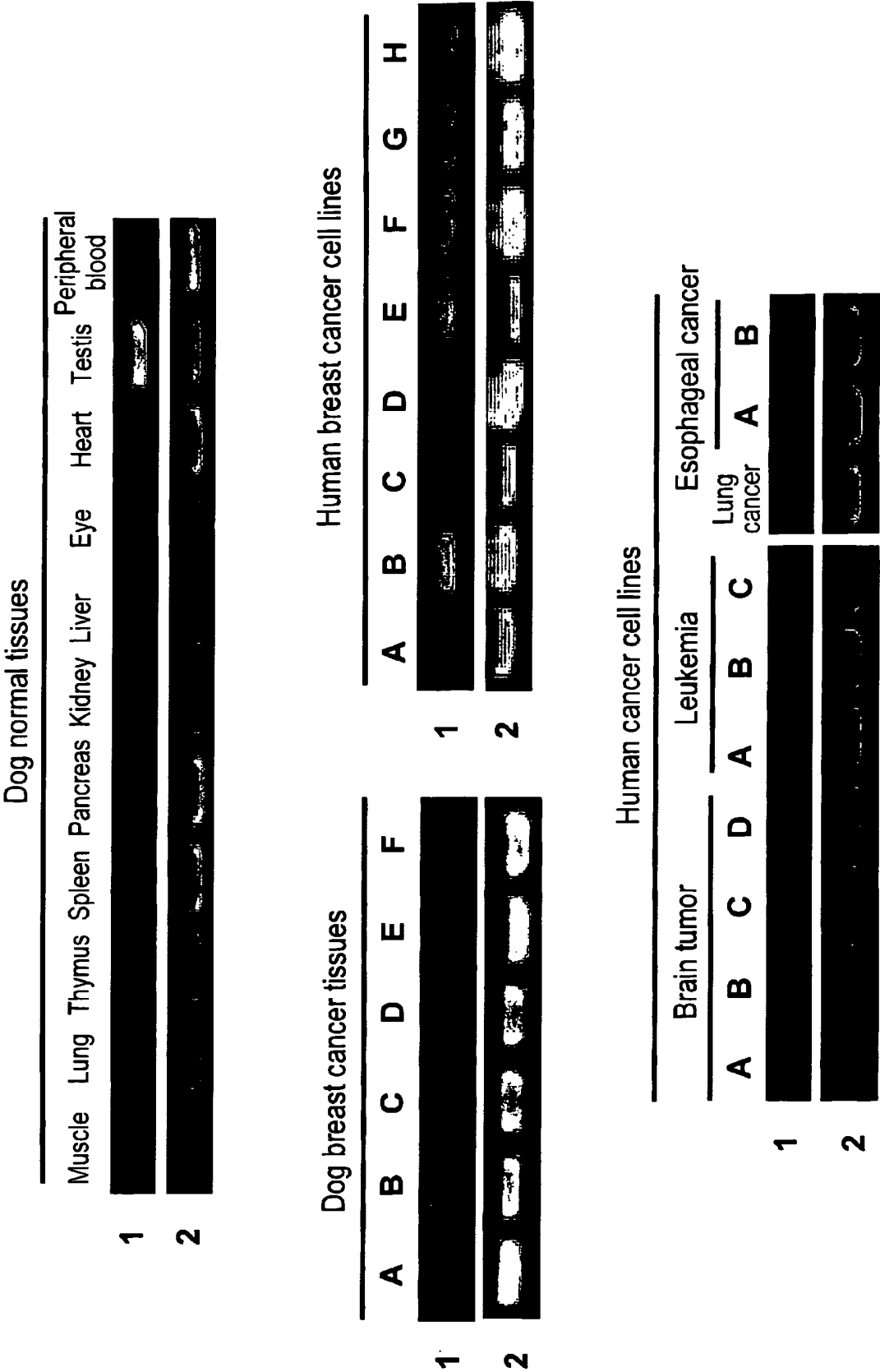
Revendications

1. Anticorps ou un fragment de celui-ci, qui comprend une région variable de chaîne lourde comprenant des CDRs 1 à 3 représentées par les SEQ ID NOS : 39, 40 et 41 respectivement et une région variable de chaîne légère comprenant des CDRs 1 à 3 représentées par les SEQ ID NOS : 43, 44 et 45 respectivement, et possède une réactivité immunologique avec une protéine CAPRIN-1.
2. Anticorps ou fragment de celui-ci selon la revendication 1, qui est un anticorps humain, un anticorps humanisé, un anticorps chimérique, un anticorps à une seule chaîne ou un anticorps bispécifique.
3. Composition pharmaceutique comprenant l'anticorps ou un fragment de celui-ci de la revendication 1 ou de la revendication 2 comme ingrédient actif.

55

4. Composition pharmaceutique selon la revendication 3, comprenant en outre un agent anti-tumoral.
5. Combinaison pharmaceutique, comprenant la composition pharmaceutique de la revendication 3 et une composition pharmaceutique contenant un agent anti-tumoral.
6. Anticorps ou fragment de celui-ci selon la revendication 1 ou la revendication 2, la composition pharmaceutique de la revendication 3 ou la revendication 4 ou la combinaison pharmaceutique de la revendication 5, pour utilisation comme médicament.
7. Anticorps ou fragment de celui-ci selon la revendication 1 ou la revendication 2, la composition pharmaceutique de la revendication 3 ou de la revendication 4 ou la combinaison pharmaceutique de la revendication 5, pour utilisation dans une méthode de traitement et/ou de prévention d'un cancer.
8. Anticorps, fragment ou composition pharmaceutique pour utilisation selon la revendication 7, où la méthode comprend l'administration à un sujet de l'anticorps ou d'un fragment de celui-ci de la revendication 1 ou de la revendication 2 ou de la composition pharmaceutique de la revendication 3 et d'un agent anti-tumoral.
9. Agent anti-tumoral pour utilisation dans une méthode de traitement et/ou de prévention d'un cancer, où la méthode comprend l'administration à un sujet de l'agent anti-tumoral et d'un anticorps ou fragment de celui-ci selon la revendication 1 ou la revendication 2 ou de la composition pharmaceutique de la revendication 3.
10. Anticorps, fragment, composition pharmaceutique, combinaison pharmaceutique ou agent anti-tumoral pour utilisation selon l'une quelconque des revendications 7 à 9, où le cancer est le cancer du sein, une tumeur cérébrale, la leucémie, un lymphome, le cancer du poumon, un mastocytome, le cancer du rein, le cancer du col utérin, le cancer de la vessie, le cancer de l'oesophage, le cancer gastrique ou le cancer colorectal.

Fig. 1



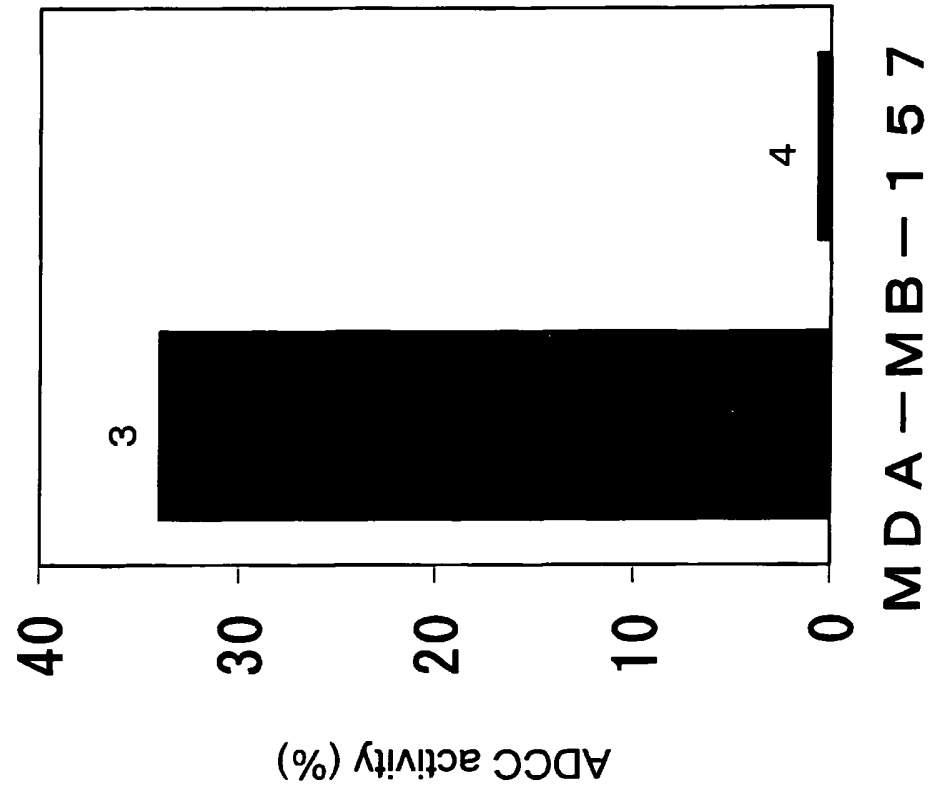
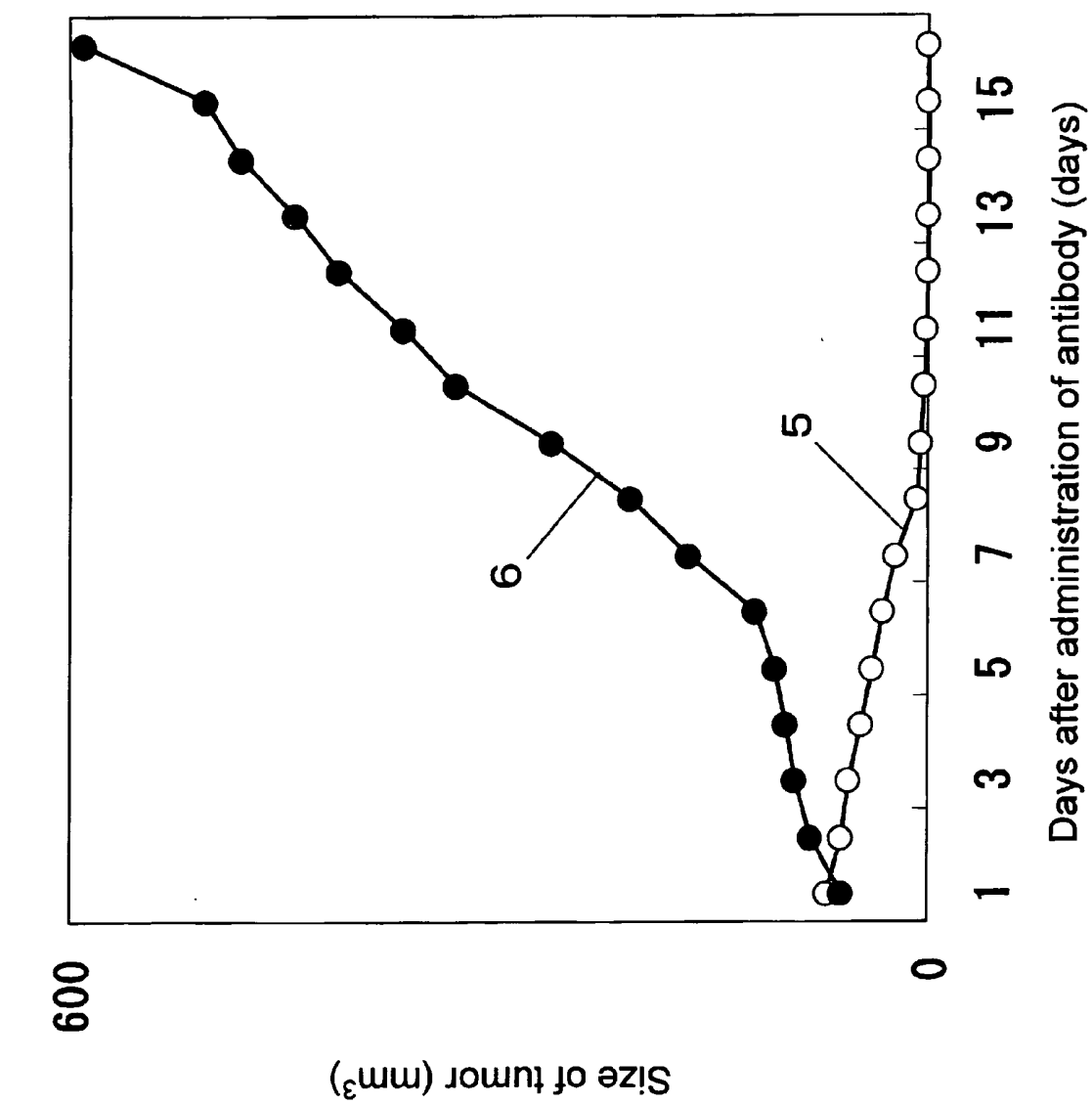


Fig. 2



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GYÓGYÁSZATI KÉSZÍTMÉNY RÁK KEZELÉSÉRE ÉS/VAGY MEGELŐZÉSÉRE

Szabadalmi igénypontok

1. Antitest vagy annak fragmense, amely tartalmaz olyan nehézlánc variábilis régiót, amely tartalmazza a SEQ ID NO: 39 (azaz a 39-es azonosítási számú szekvencia) szerinti CDR1-et, a SEQ ID NO: 40 szerinti CDR2-t és a SEQ ID NO: 41 szerinti CDR3-at, és olyan könnyűlánc variábilis régiót, amely tartalmazza a SEQ ID NO: 43 szerinti CDR1-et, a SEQ ID NO: 44 szerinti CDR2-t és a SEQ ID NO: 45 szerinti CDR3-at, és immunológiai reaktivitást mutat CAPRIN-1 fehérjével.
2. Az 1. igénypont szerinti antitest vagy annak fragmense, ahol az antitest humán antitest, humanizált antitest, kíméra antitest, egyláncú antitest vagy bispecifikus antitest.
3. Gyógyászati készítmény, amely hatóanyagként tartalmaz az 1. vagy 2. igénypont szerinti antitestet vagy antitest-fragmenst.
4. A 3. igénypont szerinti gyógyászati készítmény, amely tumorellenes ágens is tartalmaz.
5. Gyógyászati kombináció, amely tartalmazza a 3. igénypont szerinti gyógyászati készítményt, valamint tumorellenes ágens tartalmazó gyógyászati készítményt.
6. Az 1. vagy 2. igénypont szerinti antitest vagy antitest-fragmens, a 3. vagy 4. igénypont szerinti gyógyászati készítmény, vagy az 5. igénypont szerinti gyógyászati kombináció gyógyszerként történő alkalmazásra.

7. Az 1. vagy 2. igénypont szerinti antitest vagy antitest-fragmens, a 3. vagy 4. igénypont szerinti gyógyászati készítmény, vagy az 5. igénypont szerinti gyógyászati kombináció rák kezelésére és/vagy megelőzésére szolgáló eljárásban történő alkalmazásra.
8. Az antitest, a fragmens vagy a gyógyászati készítmény alkalmazásra a 7. igénypont szerint, ahol az eljárás tartalmazza, hogy beadjuk egy alanynak az 1. vagy 2. igénypont szerinti antitestet vagy antitest-fragmenst vagy a 3. igénypont szerinti gyógyászati készítményt és egy tumorellenes ágens.
9. Tumorellenes ágens rák kezelésére és/vagy megelőzésére szolgáló eljárásban történő alkalmazásra, ahol az eljárás tartalmazza, hogy beadjuk egy alanynak a tumorellenes ágens és az 1. vagy 2. igénypont szerinti antitestet vagy antitest-fragmenst vagy a 3. igénypont szerinti gyógyászati készítményt.
10. Az antitest, fragmens, gyógyászati készítmény, gyógyászati kombináció vagy tumorellenes ágens alkalmazásra a 7-9. igénypontok bármelyike szerint, ahol a rák mellrák, agytumor, leukémia, limfóma, tüdőrák, masztocitóma, veserák, méhnyakrák, húgyhólyagrák, nyelőcsőrák, gyomorrák vagy kolorektális rák.