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(54) Titre : AGENT INDUCTEUR D'IMMUNITE SERVANT A LA PROPHYLAXIE OU AU TRAITEMENT DE CANCER
EXPRIMANT LA PDS5A
(54) Title: IMMUNITY-INDUCING AGENT FOR PROPHYLAXIS OR TREATMENT OF A PDS5A-EXPRESSING CANCER

(57) **Abrégé/Abstract:**

An immunity-inducing agent comprising as an effective ingredient(s) a polypeptide(s) selected from the polypeptides: (a) a polypeptide consisting essentially of not less than 7 consecutive amino acids in any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 in SEQUENCE LISTING; (b) a polypeptide having a sequence identity of not less than 90% with the polypeptide (a) and consisting essentially of not less than 7 amino acids; and (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof; which polypeptide(s) has/have an immunity-inducing activity/activities, or as an effective ingredient(s) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding the polypeptide(s) and is/are capable of expressing the polypeptide(s) in vivo, is useful as a therapeutic and/or prophylactic agent for cancer, and/or the like.

ABSTRACT

An immunity-inducing agent comprising as an effective ingredient(s) a polypeptide(s) selected from the polypeptides: (a) a polypeptide consisting essentially of not less than 7 consecutive amino acids in any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 in SEQUENCE LISTING; (b) a polypeptide having a sequence identity of not less than 90% with the polypeptide (a) and consisting essentially of not less than 7 amino acids; and (c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof; which polypeptide(s) has/have an immunity-inducing activity/activities, or as an effective ingredient(s) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding the polypeptide(s) and is/are capable of expressing the polypeptide(s) in vivo, is useful as a therapeutic and/or prophylactic agent for cancer, and/or the like.

DESCRIPTION

Immunity-Inducing Agent for Prophylaxis or Treatment of a PDS5A-Expressing Cancer

TECHNICAL FIELD

[0001]

- 5 The present invention relates to a novel immunity-inducing agent useful as a therapeutic and/or prophylactic agent for cancer.

BACKGROUND ART

[0002]

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

[0003]

- 20 In immunotherapy, in order to reduce side effects, it is necessary that the peptide or protein to be recognized as the antigen exist hardly in normal cells and exist specifically in cancer cells. In 1991, Boon et al. of Ludwig Institute in Belgium isolated a human melanoma antigen MAGE 1, which is recognized by CD8-positive T cells, by a cDNA-expression cloning method using an autologous cancer cell line and cancer-reactive T cells (Non-patent Document 1).
25 Thereafter, the SEREX (serological identifications of antigens by recombinant expression cloning) method, wherein tumor antigens recognized by antibodies produced in the living

body of a cancer patient in response to the cancer of the patient himself are identified by application of a gene expression cloning method, was reported (Patent Document 1, Non-patent Document 2), and several cancer antigens have been isolated by this method. Using a part of the cancer antigens as targets, clinical tests for cancer immunotherapy have started.

[0004]

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

[0005]

PDS5A (PDS5, regulator of cohesion maintenance, homolog A) is a protein also called SSC-112 which was identified as a cell cycle regulator involved in distribution of chromosomes, and reported to show higher expression in nasopharyngeal carcinoma, renal cancer, liver cancer and a certain type of breast cancer cells, compared to normal tissues (Patent Document 2, Non-patent Documents 3 to 5). It has been reported that the growth of cancer cells can be suppressed by suppressing expression of PDS5A in cancer cells using an antisense nucleic acid, ribozyme or siRNA against the PDS5A gene or using an antibody that specifically binds to the PDS5A protein, and that cancer cells can be induced to cause apoptosis.

by administering the full-length PDS5A protein or a partial peptide of the PDS5A protein (Patent Document 3). Further, in Patent Document 3, increase in the mRNA level of the PDS5A protein in cancer cells was confirmed. However, there is no report suggesting that the PDS5A protein and a partial peptide of the protein has an action to induce immunity against cancer cells and hence the protein and a partial peptide of the protein is useful for therapy or prophylaxis of cancer, and whether or not the PDS5A protein has a function as a marker that can be used for diagnosis of cancer has not been confirmed.

PRIOR ART DOCUMENTS

[0006]

Patent Documents

[Patent Document 1] US 5698396 B

[Patent Document 2] WO2006/109943

[Patent Document 3] WO2002/081641

[0007]

Non-patent Documents

[Non-patent Document 1] Science, 254: 1643-1647 (1991)

[Non-patent Document 2] Proc. Natl. Acad. Sci. USA, 92: 11810-11813 (1995)

[Non-patent Document 3] Gene. 17; 328: 187-96 (2004)

[Non-patent Document 4] J. Cell. Sci. 15; 118 (Pt 10): 2133-41 (2005)

[Non-patent Document 5] J. Cancer Res. Clin. Oncol.: 134(4):453-62 (2008)

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0008]

The present invention aims to discover a novel polypeptide useful for a therapeutic and/or prophylactic agent for cancer or useful for detection of cancer, to

provide the polypeptide for use in an immunity-inducing agent or in detection of cancer

MEANS FOR SOLVING THE PROBLEMS

[0009]

5 By the SEREX method using a canine breast cancer-derived cDNA library and serum obtained from a tumor-bearing dog, the present inventors intensively studied to obtain a cDNA encoding a protein which binds to antibodies existing in the serum derived from a tumor-bearing living body, and, based on the cDNA, the canine PDS5 protein, a regulator of cohesion maintenance, homolog A (hereinafter
10 also referred to as PDS5A), having the amino acid sequence shown in SEQ ID NO:2 was prepared. Further, based on human and murine homologous genes of the obtained gene, human PDS5A having the amino acid represented by SEQ ID NO:4 or 44 (SEQ ID NO:4 corresponds to a partial sequence of SEQ ID NO:44) and murine PDS5A having the amino acid sequence shown in SEQ ID NO:6 were prepared.

15 The present inventors then discovered that that these PDS5A are specifically expressed in tissues or cells of breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, perianal adenocarcinoma, neuroblastoma and leukemia. Further, the present inventors discovered that, by administration of these PDS5A to a living body, immunocytes against PDS5A can be induced in the living
20 body, and a tumor in the living body expressing PDS5A can be regressed. Further, the present inventors discovered that a recombinant vector which can express a polynucleotide encoding the full-length PDS5A protein or a fragment thereof can induce an anti-tumor effect against cancer expressing PDS5A in the living body.

[0010]

25 Further, the present inventors discovered that a partial peptide of PDS5A has a capacity to be presented by antigen-presenting cells, thereby allowing activation and growth of cytotoxic T cells specific to the peptide (immunity-inducing activity),

and therefore that the peptide is useful for therapy and/or prophylaxis of cancer, and, further, that antigen-presenting cells which have contacted with the peptide and T cells which have contacted with the antigen-presenting cells are useful for therapy and/or prophylaxis of cancer, thereby completing the present invention.

5 [0011]

Thus, the present invention has the following characteristics.

[0012]

(1) An immunity-inducing agent comprising as an effective ingredient(s) at least one polypeptide selected from the polypeptides (a) to (c) below, the polypeptide(s) having an immunity-inducing activity/activities, or as an effective ingredient(s) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding the polypeptide(s) and is/are capable of expressing the polypeptide(s) in vivo:

(a) a polypeptide consisting essentially of not less than 7 consecutive amino acids in any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 in SEQUENCE LISTING;

(b) a polypeptide having a sequence identity of not less than 90% with the polypeptide (a) and consisting essentially of not less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence thereof.

20 [0013]

(2) The immunity-inducing agent according to (1), wherein the polypeptide (b) has a sequence identity of not less than 95% with the polypeptide (a).

[0014]

(3) The immunity-inducing agent according to (1), wherein each of the polypeptide(s) having an immunity-inducing activity/activities is a polypeptide consisting essentially of not less than 7 consecutive amino acids in any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, or a

polypeptide comprising the polypeptide as a partial sequence thereof; or a polypeptide having the same amino acid sequence as a polypeptide consisting essentially of not less than 7 consecutive amino acids in any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 except that one or several amino acids are deleted, substituted and/or added, or a polypeptide comprising the polypeptide as a partial sequence thereof.

[0015]

(4) The immunity-inducing agent according to (3), wherein each of the polypeptide(s) having an immunity-inducing activity/activities is a polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 in SEQUENCE LISTING.

[0016]

(5) The immunity-inducing agent according to (3), wherein each of the polypeptide(s) having an immunity-inducing activity/activities is a polypeptide consisting essentially of not less than 7 consecutive amino acids in the region of aa111-140, aa211-240, aa248-278, aa327-357, aa459-522, aa909-972, aa959-1022, aa994-1057 or aa1018-1080 in any one of the amino acid sequences shown in SEQ ID NOs:2, 6, 8, 10, 12 and 44 in SEQUENCE LISTING, or a polypeptide comprising the polypeptide as a partial sequence thereof; or a polypeptide having the same amino acid sequence as a polypeptide consisting essentially of not less than 7 consecutive amino acids in the region of aa111-140, aa211-240, aa248-278, aa327-357, aa459-522, aa909-972, aa959-1022, aa994-1057 or aa1018-1080 in any one of the amino acid sequences shown in SEQ ID NOs:2, 6, 8, 10, 12 and 44 in SEQUENCE LISTING except that one or several amino acids are deleted, substituted and/or added, or a polypeptide comprising the polypeptide as a partial sequence thereof.

[0017]

(6) The immunity-inducing agent according to (5), wherein each of the

polypeptide(s) having an immunity-inducing activity/activities is a polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:27 to 35 in SEQUENCE LISTING, or a polypeptide comprising the polypeptide as a partial sequence thereof and having 10 to 12 amino acid residues; or a polypeptide having the same amino acid sequence as a polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:27 to 35 in SEQUENCE LISTING except that one or several amino acids are deleted, substituted and/or added, or a polypeptide comprising the polypeptide as a partial sequence thereof and having 10 to 12 amino acid residues.

10 [0018]

(7) The immunity-inducing agent according to any one of (1) to (6), for prophylaxis of a cancer in an animal.

[0019]

15 (8) The immunity-inducing agent according to (5) or (6), for therapy of a cancer in an animal.

[0020]

(9) The immunity-inducing agent according to (7) or (8), wherein the cancer is a cancer expressing PDS5A.

[0021]

20 (10) The immunity-inducing agent according to any one of (7) to (9), wherein the cancer is breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, perianal adenocarcinoma, neuroblastoma or leukemia.

[0022]

25 (11) The immunity-inducing agent according to any one of (1) to (10), further comprising an immunoenhancer.

[0023]

(12) An isolated antigen-presenting cell comprising a complex between the

polypeptide having an immunity-inducing activity and an MHC molecule.

[0024]

(13) An isolated T cell which selectively binds to a complex between the polypeptide having an immunity-inducing activity and an MHC molecule.

5 [0025]

(14) A polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:27 to 35 in SEQUENCE LISTING, or a polypeptide comprising the polypeptide as a partial sequence thereof and having 10 to 12 amino acid residues; or a polypeptide having the same amino acid sequence as a polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:27 to 35 in SEQUENCE LISTING except that one or several amino acids are deleted, substituted and/or added, or a polypeptide comprising the polypeptide as a partial sequence thereof and having 10 to 12 amino acid residues, which polypeptide has an immunity-inducing activity.

[0026]

15 (15) A method for detecting a cancer, the method comprising measurement of expression of a polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 in SEQUENCE LISTING or a polypeptide having a sequence identity of not less than 90% with the polypeptide, in a sample separated from a living body.

20 [0027]

(16) A method for inducing immunity, the method comprising administering to an individual at least one polypeptide selected from the polypeptides (a) to (c) below, the polypeptide(s) having an immunity-inducing activity/activities, or a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding the polypeptide(s) and is/are capable of expressing the polypeptide(s) in vivo:

25 (a) a polypeptide consisting essentially of not less than 7 consecutive amino acids in any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12

and 44 in SEQUENCE LISTING;

(b) a polypeptide having a sequence identity of not less than 90% with the polypeptide (a) and consisting essentially of not less than 7 amino acids; and

(c) a polypeptide comprising the polypeptide (a) or (b) as a partial sequence
5 thereof.

[0027A]

The present invention as claimed relates to:

- an immunity-inducing agent for prophylaxis or therapy of a PDS5A-
expressing cancer in an animal, the agent comprising: (a) at least one polypeptide, the amino
10 acid sequence of which is shown in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, said
polypeptide(s) having an immunity-inducing activity/activities, or (b) a recombinant vector(s)
which comprise(s) a polynucleotide(s) encoding said polypeptide(s) as defined in (a), and
which express(es) said polypeptide(s) in vivo;

- an immunity-inducing agent for prophylaxis or therapy of a PDS5A-
15 expressing cancer in an animal, the agent comprising: (a) at least one polypeptide, the amino
acid sequence of which is shown in any one of SEQ ID NOs:27 to 35, said polypeptide(s)
having an immunity-inducing activity/activities, or (b) a recombinant vector(s) which
comprise(s) a polynucleotide(s) encoding said polypeptide(s) defined in (a), and which
express(es) said polypeptide(s) in vivo;

20 - a polypeptide, the amino acid sequence of which is shown in any one of
SEQ ID NOs:27, 28 and 30 to 35;

- a method for detecting a PDS5A-expressing cancer, said method comprising
measurement of anti PDS5A antibodies that bind specifically to a polypeptide, the amino acid
sequence of which is shown in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, in a sample
25 separated from a living body;

- use of: (a) at least one polypeptide, the amino acid sequence of which is shown in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, said polypeptide(s) having an immunity-inducing activity/activities, or (b) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) as defined in (a), and which express(es) said polypeptide(s) in vivo;
 5 for inducing immunity against a PDS5A-expressing cancer; and

- use of: (a) at least one polypeptide, the amino acid sequence of which is shown in any one of SEQ ID NOs:27 to 35, said polypeptide(s) having an immunity-inducing activity/activities, or (b) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) as defined in (a), and which express(es) said polypeptide(s) in vivo; for
 10 inducing immunity against a PDS5A-expressing cancer.

EFFECT OF THE INVENTION

[0028]

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

BRIEF DESCRIPTION OF THE DRAWINGS

[0029]

20 Fig. 1 shows the expression patterns of the identified PDS5A gene in canine normal tissues, tumor tissues and tumor cell lines. Reference numeral 1, the expression patterns of the canine PDS5A gene in various canine tissues and cell lines; reference numeral 2, the expression patterns of the canine GAPDH gene in various canine tissues and cell lines.

25 Fig. 2 shows the expression patterns of the identified PDS5A gene in human normal tissues, tumor tissues and tumor cell lines. Reference numeral 3, the expression patterns of the human PDS5A gene in various human tissues and cell lines; reference numeral 4, the expression patterns of the human GAPDH gene in various human tissues and cell lines.

Fig. 3 shows the expression patterns of the identified PDS5A gene in murine normal tissues, tumor tissues and tumor cell lines. Reference numeral 5, the

expression patterns of the murine PDS5A gene in various murine tissues and cell lines; reference numeral 6, the expression patterns of the murine GAPDH gene in various murine tissues and cell lines.

Fig. 4 is a graph showing that an anti-tumor effect (therapeutic model: neuroblastoma cell line) was observed by administration of PDS5A. Immunization was carried out with a vector alone or a plasmid encoding PDS5A using a gene gun, and the evaluation was carried out based on the area of the cancerous part and the ratio of living mice. For each group, 10 individuals of mice were used. The mice were observed twice a week. The data are represented by the mean value $\pm$ SD. Reference numeral 7, the group wherein a plasmid vector was administered; reference numeral 8, the group wherein a plasmid encoding PDS5A was administered.

Fig. 5 is a graph showing that an anti-tumor effect (prophylactic model: neuroblastoma cell line) was observed by administration of PDS5A. Immunization was carried out with a vector alone or a plasmid encoding PDS5A using a gene gun, and the evaluation was carried out based on the area of the cancerous part and the ratio of living mice. For each group, 10 individuals of mice were used. The mice were observed twice a week. The data are represented by the mean value $\pm$ SD. Reference numeral 9, the group wherein a plasmid vector was administered; reference numeral 10, the group wherein a plasmid encoding PDS5A was administered.

Fig. 6 shows the ratio of living mice in the experiment in Fig. 4. Reference numeral 11, the group wherein a plasmid vector was administered; reference numeral 12, the group wherein a plasmid encoding PDS5A was administered.

Fig. 7 shows the ratio of living mice in the experiment in Fig. 5. Reference numeral 13, the group wherein a plasmid vector was administered; reference numeral 14, the group wherein a plasmid encoding PDS5A was administered.

Fig. 8 is a graph showing that an anti-tumor effect (therapeutic model: colon

cancer cell line) was observed by administration of PDS5A. Immunization was carried out with a vector alone or a plasmid encoding PDS5A using a gene gun, and the evaluation was carried out based on the area of the cancerous part and the ratio of living mice. For each group, 10 individuals of mice were used. The mice were
5 observed twice a week. The data are represented by the mean value $\pm$ SD. Reference numeral 15, the group wherein a plasmid vector was administered; reference numeral 16, the group wherein a plasmid encoding PDS5A was administered.

Fig. 9 is a graph showing that an anti-tumor effect (prophylactic model: colon
10 cancer cell line) was observed by administration of PDS5A. Immunization was carried out with a vector alone or a plasmid encoding PDS5A using a gene gun, and the evaluation was carried out based on the area of the cancerous part and the ratio of living mice. For each group, 10 individuals of mice were used. The mice were observed twice a week. The data are represented by the mean value $\pm$ SD.
15 Reference numeral 17, the group wherein a plasmid vector was administered; reference numeral 18, the group wherein a plasmid encoding PDS5A was administered.

Fig. 10 shows the ratio of living mice in the experiment in Fig. 8. Reference numeral 19, the group to which a plasmid vector was administered; reference
20 numeral 20, the group to which a plasmid encoding PDS5A was administered.

Fig. 11 shows the ratio of living mice in the experiment in Fig. 9. Reference numeral 21, the group to which a plasmid vector was administered; reference numeral 22, the group to which a plasmid encoding PDS5A was administered.

Fig. 12 is a diagram showing that CD8-positive T cells specific to each of the
25 polypeptides having the amino acid sequences shown in SEQ ID NOs:27 to 35 in SEQUENCE LISTING recognize the complex between the polypeptide and HLA-A0201, and produce IFN- γ . In Fig. 12, the reference numerals 25 to 33 along the

abscissa indicate the abilities of HLA-A0201-positive CD8-positive T cells to produce IFN- γ in response to stimulation by T2 cells pulsed with the respective peptides of SEQ ID NOs:27 to 35. The reference numeral 23 shows a result obtained when the above treatment was carried out without addition of a polypeptide, and the reference numeral 24 shows a result obtained when the above treatment was carried out with addition of the polypeptide shown in SEQ ID NO:36, which is outside the scope of the present invention.

Fig. 13 is a diagram showing the cytotoxic activities, against cancer cells, of CD8-positive T cells specific to each of the polypeptides having the amino acid sequences shown in SEQ ID NOs:27 to 35 in SEQUENCE LISTING. In Fig. 13, the reference numerals 36 to 44 along the abscissa indicate the cytotoxic activities, against T98G cells, of HLA-A0201-positive CD8-positive T cells stimulated with the respective peptides of SEQ ID NOs:27 to 35. The reference numeral 34 shows the cytotoxic activity of CD8-positive T cells induced without addition of a polypeptide, and the reference numeral 35 shows the cytotoxic activity of CD8-positive T cells induced using a negative control peptide (SEQ ID NO:36).

BEST MODE FOR CARRYING OUT THE INVENTION

[0030]

Examples of the polypeptide contained in the immunity-inducing agent of the present invention as an effective ingredient include the followings. In the present invention, the term "polypeptide" means a molecule formed by a plurality of amino acids linked together by peptide bonds, and includes not only polypeptide molecules having large numbers of amino acids constituting them, but also low-molecular-weight molecules having small numbers of amino acids (oligopeptides), and full-length proteins. In the present invention, the full-length PDS5A proteins having the amino acid sequences shown in SEQ ID NO:2, 4, 6, 8, 10, 12 and 44 are also included therein.

[0031]

(a) A polypeptide which consists essentially of not less than 7 consecutive amino acids in a polypeptide having the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 in SEQUENCE LISTING, and has an immunity-inducing activity.

(b) a polypeptide which has a sequence identity of not less than 90% with the polypeptide (a), consists essentially of not less than 7 amino acids, and has an immunity-inducing activity.

(c) a polypeptide which comprises the polypeptide (a) or (b) as a partial sequence thereof, and has an immunity-inducing activity.

[0032]

In the present invention, the term "having an amino acid sequence" means that amino acid residues are arrayed in such an order. Therefore, for example, "polypeptide having the amino acid sequence shown in SEQ ID NO:2" means the polypeptide having the amino acid sequence of Met Asp Phe Thr ... (snip) ... Asp Leu Gln Arg shown in SEQ ID NO:2, which polypeptide has a size of 1337 amino acid residues. Further, for example, "polypeptide having the amino acid sequence shown in SEQ ID NO:2" may be abbreviated as "polypeptide of SEQ ID NO:2". This also applies to the term "having a base sequence". In this case, the term "having" may be replaced with the expression "essentially consisting of".

[0033]

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

[0034]

Whether or not the polypeptide has an immunity-inducing activity can be confirmed using, for example, the known ELISPOT assay. More particularly, for example, as described in the Examples below, cells such as peripheral blood

mononuclear cells are obtained from a living body to which a polypeptide whose immunity-inducing activity is to be evaluated was administered, which cells are then cocultured with the polypeptide, followed by measuring the amount(s) of a cytokine(s) produced by the cells using a specific antibody/antibodies, thereby measuring the number of immunocytes in the cells, which enables evaluation of the immunity-inducing activity.

[0035]

Alternatively, as described in the later-mentioned Examples, when a recombinant polypeptide in any of (a) to (c) described above is administered to a tumor-bearing animal, the tumor can be regressed by its immunity-inducing activity. Thus, the above immunity-inducing activity can be evaluated also as an ability to suppress the growth of cancer cells or to cause reduction or disappearance of a cancer tissue (tumor) (hereinafter referred to as "anti-tumor activity"). The anti-tumor activity of a polypeptide can be confirmed by, for example, as more particularly described in the Examples below, observation of whether or not a tumor is reduced when the polypeptide was actually administered to a tumor-bearing living body.

[0036]

Alternatively, the anti-tumor activity of a polypeptide can be evaluated also by observation of whether or not T cells stimulated with the polypeptide (that is, T cells brought into contact with antigen-presenting cells presenting the polypeptide) show a cytotoxic activity against tumor cells in vitro. The contact between the T cells and the antigen-presenting cells can be carried out by coculture of the both in a liquid medium, as mentioned below. Measurement of the cytotoxic activity can be carried out by, for example, the known method called ^{51}Cr release assay described in Int. J. Cancer, 58: p 317, 1994. In cases where the polypeptide is to be used for therapy and/or prophylaxis of cancer, the evaluation of the immunity-inducing activity is preferably carried out using the anti-tumor activity as an index, although

the index is not restricted.

[0037]

The amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44 in SEQUENCE LISTING are the amino acid sequences of the PDS5A proteins which were isolated, by the SEREX method using a canine testis-derived cDNA library and serum of a tumor-bearing dog, as a polypeptide that specifically binds to an antibody existing in the serum of the tumor-bearing dog and homologous factors of the polypeptide in human (SEQ ID NOs:4 and 44), mouse (SEQ ID NO:6), cow (SEQ ID NO:8), horse (SEQ ID NO:10) and chicken (SEQ ID NO:12) (see Example 1).

Human PDS5A, which is a human homologous factor of canine PDS5A, has a sequence identity of 94% in terms of the base sequence and 99% in terms of the amino acid sequence; murine PDS5A, which is a murine homologous factor, has a sequence identity of 91% in terms of the base sequence and 99% in terms of the amino acid sequence; bovine PDS5A, which is a bovine homologous factor, has a sequence identity of 95% in terms of the base sequence and 99% in terms of the amino acid sequence; equine PDS5A, which is an equine homologous factor, has a sequence identity of 96% in terms of the base sequence and 99% in terms of the amino acid sequence; and chicken PDS5A, which is a chicken homologous factor, has a sequence identity of 83% in terms of the base sequence and 98% in terms of the amino acid sequence.

[0038]

The polypeptide (a) is a polypeptide which consists essentially of not less than 7 consecutive, preferably 8, 9 or not less than 10 consecutive amino acids in the polypeptide having the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44, and has an immunity-inducing activity. The polypeptide especially preferably has the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44. As is known in the art, a polypeptide having not less than about 7 amino acid residues can

exert its antigenicity and immunogenicity. Thus, a polypeptide having not less than 7 consecutive amino acid residues in the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 can have an immunity-inducing activity, so that it can be used for preparation of the immunity-inducing agent of the present invention.

5 [0039]

As a principle of immune induction by administration of a cancer antigenic polypeptide, the following process is known: a polypeptide is incorporated into an antigen-presenting cell and then degraded into smaller fragments by peptidases in the cell, followed by presentation of the fragments on the surface of the cell. The fragments are then recognized by a cytotoxic T cell or the like, which selectively kills cells presenting the antigen. The size of the polypeptide presented on the surface of the antigen-presenting cell is relatively small and about 7 to 30 amino acids. Therefore, from the viewpoint of presenting thereof on the surface of the antigen-presenting cell, one preferred mode of the above-described polypeptide (a) is a polypeptide composed of about 7 to 30 consecutive amino acids in the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44, and more preferably, a polypeptide composed of about 8 to 30 or about 9 to 30 amino acids is sufficient as the polypeptide (a). In some cases, these relatively small polypeptides are presented directly on the surface of the antigen-presenting cell without being incorporated into the antigen-presenting cells.

20 [0040]

Further, since a polypeptide incorporated into an antigen-presenting cell is cleaved at random sites by peptidases in the cell to yield various polypeptide fragments, which are then presented on the surface of the antigen-presenting cell, administration of a large polypeptide such as the full-length region of SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 inevitably causes production of polypeptide fragments by degradation thereof in the antigen-presenting cell, which fragments are effective for

immune induction via the antigen-presenting cell. Therefore, also for immune induction via antigen-presenting cells, a large polypeptide can be preferably used, and the polypeptide may be composed of not less than 30, preferably not less than 100, more preferably not less than 200, still more preferably not less than 250 amino acids. The polypeptide may be still more preferably composed of the full-length region of SEQ ID NO:2, 4, 6, 8, 10, 12 or 44.

[0041]

Further, the polypeptides of the present invention can be checked with a checking medium by which epitope peptides having binding motifs of various types of HLA and consisting essentially of 8 to 12, preferably 9 to 10 amino acids can be searched, for example, HLA Peptide Binding Predictions (http://bimas.dcrt.nih.gov/molbio/hla_bind/index.html) in Bioinformatics & Molecular Analysis Selection (BIMAS), to screen peptides which may be epitope peptides. More particularly, a polypeptide consisting essentially of not less than 7 consecutive amino acids in the region of amino acid residue positions aa111-140, aa211-240, aa248-278, aa327-357, aa459-522, aa909-972, aa959-1022, aa994-1057 or aa1018-1080 in the amino acid sequence shown in SEQ ID NO:2, 6, 8, 10, 12 or 44 is preferred, and, in the polypeptide of SEQ ID NO:4 or 44, the polypeptide shown in any of SEQ ID NOs:27 to 35, or a polypeptide which comprises a polypeptide having the amino acid sequence shown in any of SEQ ID NOs:27 to 35 as a partial sequence and has 10 to 12 amino acid residues is more preferred.

[0042]

The polypeptide (b) is the same polypeptide as the polypeptide (a) except that a small number of (preferably, one or several) amino acid residues are substituted, deleted and/or inserted, which has a sequence identity of not less than 90%, preferably not less than 95%, more preferably not less than 98%, still more preferably not less than 99% or not less than 99.5% to the original sequence and has an

immunity-inducing activity. It is well known in the art that, in general, there are cases where a protein antigen retains almost the same antigenicity as the original protein even if the amino acid sequence of the protein is modified such that a small number of amino acids are substituted, deleted and/or inserted. Therefore, since the polypeptide (b) may also exert an immunity-inducing activity, it can be used for preparation of the immunity-inducing agent of the present invention. Further, the polypeptide (b) is also preferably the same polypeptide as one having the amino acid sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 except that one or several amino acid residues are substituted, deleted and/or inserted. As used herein, the term "several" means an integer of 2 to 10, preferably an integer of 2 to 6, more preferably an integer of 2 to 4.

[0043]

As used herein, the term "sequence identity" of amino acid sequences or base sequences means the value calculated by aligning two amino acid sequences (or base sequences) to be compared such that the number of matched amino acid residues (or bases) is maximum between the amino acid sequences (or base sequences), and dividing the number of matched amino acid residues (or the number of matched bases) by the total number of amino acid residues (or the total number of bases), which value is represented as a percentage. When the alignment is carried out, a gap(s) is/are inserted into one or both of the two sequences to be compared as required. Such alignment of sequences can be carried out using a well-known program such as BLAST, FASTA or CLUSTAL W. When a gap(s) is/are inserted, the above-described total number of amino acid residues is the number of residues calculated by counting one gap as one amino acid residue. When the thus counted total number of amino acid residues is different between the two sequences to be compared, the sequence identity (%) is calculated by dividing the number of matched amino acid residues by the total number of amino acid residues in the longer

sequence.

[0044]

The 20 types of amino acids constituting naturally occurring proteins may be classified into groups in each of which similar properties are shared, for example, into neutral amino acids with side chains having low polarity (Gly, Ile, Val, Leu, Ala, Met, Pro), neutral amino acids having hydrophilic side chains (Asn, Gln, Thr, Ser, Tyr, Cys), acidic amino acids (Asp, Glu), basic amino acids (Arg, Lys, His) and aromatic amino acids (Phe, Tyr, Trp). It is known that, in most cases, substitutions of amino acids within the same group do not change the properties of the polypeptide. Therefore, in cases where an amino acid residue(s) in the polypeptide (a) of the present invention is/are substituted, the probability that the immunity-inducing activity can be maintained may be increased by introducing the substitution(s) within the same group, which is preferred.

[0045]

As the polypeptide (b), which corresponds to the above-described epitope peptide, a polypeptide which is the same as the polypeptide consisting essentially of not less than 7 consecutive amino acids in the region of aa111-140, aa211-240, aa248-278, aa327-357, aa459-522, aa909-972, aa959-1022, aa994-1057 or aa1018-1080 in any one of the amino acid sequences shown in SEQ ID NOs:2, 6, 8, 10, 12 and 44 except that one or several amino acids are deleted, substituted and/or added, or a polypeptide comprising the polypeptide as a partial sequence thereof and having an immunity-inducing activity is preferred, and, in the polypeptide of SEQ ID NO:4 or 44, a polypeptide which is the same as the polypeptide having the amino acid sequence shown in any of SEQ ID NOs:27 to 35 except that one or several amino acids are deleted, substituted and/or added, or a polypeptide comprising the polypeptide as a partial sequence and having 10 to 12 amino acid residues is more preferred.

[0046]

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

[0047]

As the polypeptide (c), which corresponds to the above-described epitope, a polypeptide comprising as a partial sequence the polypeptide consisting essentially of not less than 7 consecutive amino acids in the region of aa111-140, aa211-240, aa248-278, aa327-357, aa459-522, aa909-972, aa959-1022, aa994-1057 or aa1018-1080 in any one of the amino acid sequences shown in SEQ ID NOs:2, 6, 8, 10, 12 and 44 is preferred, and, in the polypeptide of SEQ ID NO:4 or 44, a polypeptide comprising as a partial sequence: a polypeptide which is the same as the polypeptide having the amino acid sequence shown in any of SEQ ID NOs:27 to 35 except that one or several amino acids are deleted, substituted and/or added; or a polypeptide comprising the polypeptide as a partial sequence and having 10 to 12 amino acid residues; is more preferred.

[0048]

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

which is then introduced into a host cell, followed by allowing the polypeptide to be produced in the host cell.

[0049]

The polynucleotide encoding the above polypeptide can be easily prepared by
5 a known genetic engineering technique or a conventional method using a
commercially available nucleic acid synthesizer. For example, DNA having the
base sequence shown in SEQ ID NO:1 can be prepared by carrying out PCR using a
canine chromosomal DNA or cDNA library as a template, and a pair of primers
designed such that the base sequence shown in SEQ ID NO:1 can be amplified
10 therewith. DNA having the base sequence of SEQ ID NO:3 or 43 can be similarly
prepared by using a human chromosomal DNA or cDNA library as the template.
The reaction conditions for the PCR can be set appropriately, and examples thereof
include, but are not limited to, repeating the reaction process of 94°C for 30 seconds
(denaturation), 55°C for 30 seconds to 1 minute (annealing) and 72°C for 2 minutes
15 (extension) for, for example, 30 cycles, followed by the reaction at 72°C for 7
minutes. Further, the desired DNA can be isolated by preparing an appropriate
probe(s) or primer(s) based on the information of the base sequences and the amino
acid sequences shown in SEQ ID NO:1, 3, 5, 7, 9, 11 and 43 in SEQUENCE
LISTING in the present specification, and screening a cDNA library of dog, human
20 or the like using the probe(s) or primer(s). The cDNA library is preferably prepared
from a cell, organ or tissue expressing the protein of SEQ ID NO:2, 4, 6, 8, 10, 12 or
44. The above-described operations such as preparation of a probe(s) or primer(s),
construction of a cDNA library, screening of a cDNA library and cloning of a gene of
interest are known to those skilled in the art, and can be carried out according to the
25 methods described in Molecular Cloning, Second Edition; Current Protocols in
Molecular Biology; and/or the like. From the thus obtained DNA, DNA encoding
the polypeptide (a) can be obtained. Further, since the codons encoding each amino

acid are known, the base sequence of a polynucleotide encoding a specific amino acid sequence can be easily specified. Therefore, since the base sequence of a polynucleotide encoding the polypeptide (b) or polypeptide (c) can also be easily specified, such a polynucleotide can also be easily synthesized using a commercially available nucleic acid synthesizer according to a conventional method.

[0050]

The host cells are not restricted as long as those can express the above-described polypeptide, and examples thereof include, but are not limited to, prokaryotic cells such as *E. coli*; and eukaryotic cells such as mammalian cultured cells including monkey kidney cells COS1 and Chinese hamster ovary cells CHO; budding yeast; fission yeast; silkworm cells; and *Xenopus laevis* egg cells.

[0051]

In cases where prokaryotic cells are used as the host cells, an expression vector in which an origin that enables replication of the vector in a prokaryotic cell, promoter, ribosome binding site, DNA cloning site, terminator and/or the like is/are contained is used. Examples of the expression vector for *E. coli* include the pUC system, pBluescriptII, pET expression system and pGEX expression system. By incorporating a DNA encoding the above polypeptide into such an expression vector and transforming prokaryotic host cells with the vector, followed by culturing the resulting transformants, the polypeptide encoded by the DNA can be expressed in the prokaryotic host cells. In this process, the polypeptide can also be expressed as a fusion protein with another protein.

[0052]

In cases where eukaryotic cells are used as the host cells, an expression vector for eukaryotic cells having a promoter, splicing site, poly(A) addition site and/or the like is used as the expression vector. Examples of such an expression vector include pKA1, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector,

pRS, pcDNA3, pMSG and pYES2. In the same manner as described above, by incorporating a DNA encoding the above polypeptide into such an expression vector and transforming eukaryotic host cells with the vector, followed by culturing the resulting transformants, the polypeptide encoded by the DNA can be expressed in the eukaryotic host cells. In cases where pIND/V5-His, pFLAG-CMV-2, pEGFP-N1, pEGFP-C1 or the like is used as the expression vector, the above polypeptide can be expressed as a fusion protein wherein a tag such as a His tag, FLAG tag, myc tag, HA tag or GFP was added.

[0053]

For the introduction of the expression vector into the host cells, a well-known method such as electroporation, the calcium phosphate method, the liposome method or the DEAE dextran method may be used.

[0054]

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

[0055]

The polypeptides obtained by the above method also include, as mentioned above, those in the form of a fusion protein with another arbitrary protein.

Examples thereof include fusion proteins with glutathion S-transferase (GST) and with a His tag. Such a polypeptide in the form of a fusion protein is also included within the scope of the present invention as the above-described polypeptide (c).

Further, in some cases, a polypeptide expressed in a transformed cell is modified in various ways in the cell after translation. Such a post-translationally modified polypeptide is also included within the scope of the present invention as long as it has an immunity-inducing activity. Examples of such a post-translational modification include: elimination of N-terminal methionine; N-terminal acetylation; glycosylation; limited degradation by an intracellular protease; myristoylation; isoprenylation; and phosphorylation.

[0056]

As described more particularly in the later-mentioned Examples, by administration of the polypeptide having an immunity-inducing activity or an expression vector comprising the gene encoding the polypeptide to a tumor-bearing living body, an already existing tumor can be regressed. Further, by administration of the polypeptide having an immunity-inducing activity or the gene encoding the polypeptide to a living body before occurrence of cancer, development of a tumor can be prevented. Therefore, the immunity-inducing agent of the present invention can be used as a therapeutic and/or prophylactic agent for cancer. Further, the polypeptide having an immunity-inducing activity can be used for a method of therapy and/or prophylaxis of cancer by immune induction.

[0057]

As used herein, the terms "tumor" and "cancer" mean a malignant neoplasm, and are used interchangeably

[0058]

In this case, the cancer to be treated is not restricted as long as PDS5A is expressed in the cancer, and the cancer is preferably breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, perianal adenocarcinoma, neuroblastoma or leukemia.

[0059]

The subject animal is preferably a mammal, more preferably a mammal such as a primate, pet animal, domestic animal or sport animal, especially preferably human, dog or cat.

[0060]

5 The administration route of the immunity-inducing agent of the present invention to a living body may be either oral administration or parenteral administration, and is preferably parenteral administration such as intramuscular administration, subcutaneous administration, intravenous administration or intraarterial administration. In cases where the immunity-inducing agent is used for
10 therapy of cancer, it may be administered to a regional lymph node in the vicinity of the tumor to be treated, as described in the Examples below, in order to enhance its anticancer activity. The dose may be any dose as long as the dose is effective for immune induction, and, for example, in cases where the agent is used for therapy and/or prophylaxis of cancer, the dose may be one effective for therapy and/or
15 prophylaxis of the cancer. The dose effective for therapy and/or prophylaxis of cancer is appropriately selected depending on the size and symptoms of the tumor and the like, and the effective dose is usually, 0.0001 μg to 1000 μg , preferably 0.001 μg to 1000 μg per subject animal per day, which may be administered once or in several times. The agent is preferably administered in several times, every several
20 days to several months. As concretely shown in the Examples below, the immunity-inducing agent of the present invention can cause regression of an already occurred tumor. Therefore, since the agent can exert its anticancer activity also against a small number of cancer cells at an early stage, development or recurrence of cancer can be prevented by using the agent before development of the cancer or after therapy
25 for the cancer. That is, the immunity-inducing agent of the present invention is effective for both therapy and prophylaxis of cancer.

[0061]

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

[0062]

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

[0063]

Examples of the immunoenhancer include adjuvants. Adjuvants can enhance the immune response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes, thereby enhancing the immune response and hence the anticancer action. Therefore, especially in cases where the immunity-inducing agent of the present invention is used for therapy and/or prophylaxis of cancer, the immunity-

inducing agent preferably comprises an adjuvant, in addition to the above-described polypeptide as an effective ingredient. Many types of adjuvants are well-known in the art, and any of these adjuvants may be used. Specific examples of the adjuvants include MPL (SmithKline Beecham), homologues of *Salmonella minnesota* Re 595 lipopolysaccharide obtained after purification and acid hydrolysis of the lipopolysaccharide; QS21 (SmithKline Beecham), pure QA-21 saponin purified from an extract of *Quillja saponaria*; DQS21 described in PCT application WO96/33739 (SmithKline Beecham); QS-7, QS-17, QS-18 and QS-L1 (So and 10 colleagues, "Molecules and cells", 1997, Vol. 7, p. 178-186); Freund's incomplete adjuvant; Freund's complete adjuvant; vitamin E; Montanide; alum; CpG oligonucleotides (see, for example, Kreig and 7 colleagues, Nature, Vol. 374, p. 546-549); poly-I:C and derivatives thereof (e.g., poly ICLC); and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Among these, Freund's incomplete adjuvant; Montanide; poly-I:C and derivatives thereof; and CpG oligonucleotides are preferred. The mixing ratio between the above-described adjuvant and the polypeptide is typically about 1:10 to 10:1, preferably about 1:5 to 5:1, more preferably about 1:1. However, the adjuvant is not limited to the above-described examples, and adjuvants known in the art other than those described above may also be used when the immunity-inducing agent of the present invention is administered (see, for example, Goding, "Monoclonal Antibodies: Principles and Practice, 2nd edition", 1986). Preparation methods for mixtures or emulsions of a polypeptide and an adjuvant are well-known to those skilled in the art of vaccination.

[0064]

Further, in addition to the above-described adjuvants, factors that stimulate the immune response of the subject may be used as the above-described immunoenhancer. For example, various cytokines having a property to stimulate lymphocytes and/or antigen-presenting cells may be used as the immunoenhancer in

combination with the immunity-inducing agent of the present invention. A number of such cytokines capable of enhancing the immune response are known to those skilled in the art, and examples thereof include, but are not limited to, interleukin-12 (IL-12), GM-CSF, IL-18, interferon- α , interferon- β , interferon- ω , interferon- γ , and Flt3 ligand, which have been shown to enhance the prophylactic action of vaccines. Such factors may also be used as the above-described immunoenhancer, and may be contained in the immunity-inducing agent of the present invention, or may be prepared as a separate composition to be used in combination with the immunity-inducing agent of the present invention, to be administered to a patient.

[0065]

By bringing the above-described polypeptide into contact with antigen-presenting cells in vitro, the antigen-presenting cells can be made to present the polypeptide. That is, the polypeptides (a) to (c) described above can be used as agents for treating antigen-presenting cells. Examples of the antigen-presenting cells which may be preferably used include dendritic cells and B cells having MHC class I molecules. Various MHC class I molecules have been identified and are well-known. MHC molecules in human are called HLA. Examples of HLA class I molecules include HLA-A, HLA-B and HLA-C, more specifically, HLA-A1, HLA-A0201, HLA-A0204, HLA-A0205, HLA-A0206, HLA-A0207, HLA-A11, HLA-A24, HLA-A31, HLA-A6801, HLA-B7, HLA-B8, HLA-B2705, HLA-B37, HLA-Cw0401 and HLA-Cw0602.

[0066]

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

related peptide to the culture system.

[0067]

By administering an effective amount of such dendritic cells, a response desired for therapy of a cancer can be induced. As the cells to be used, bone marrow or umbilical cord blood donated by a healthy individual, or bone marrow, peripheral blood or the like from the patient himself may be used. When autologous cells of the patient are used, high safety can be attained and serious side effects are expected to be avoided. The peripheral blood or bone marrow may be any of a fresh sample, cold-stored sample and frozen sample. As for the peripheral blood, whole blood may be cultured or the leukocyte components alone may be separated and cultured, and the latter is more efficient and thus preferred. Further, among the leukocyte components, mononuclear cells may be separated. In cases where the cells are originated from bone marrow or umbilical cord blood, the whole cells constituting the bone marrow may be cultured, or mononuclear cells may be separated therefrom and cultured. Peripheral blood, the leukocyte components thereof and bone marrow cells contain mononuclear cells, hematopoietic stem cells and immature dendritic cells, from which dendritic cells are originated, and also CD4-positive cells and the like. As for the cytokine to be used, the production method thereof is not restricted, and a naturally-occurring or recombinant cytokine or the like may be employed as long as its safety and physiological activity have been confirmed. Preferably, a preparation with assured quality for medical use is used in a minimum necessary amount. The concentration of the cytokine(s) to be added is not restricted as long as the dendritic cells are induced at the concentration, and usually, the total concentration of the cytokine(s) is preferably about 10 to 1000 ng/mL, more preferably about 20 to 500 ng/mL. The culture may be carried out using a well-known medium usually used for culture of leukocytes. The culturing temperature is not restricted as long as proliferation of the leukocytes is attained at

the temperature, and a temperature of about 37°C, which is the body temperature of human, is most preferred. The atmospheric environment during the culturing is not restricted as long as proliferation of the leukocytes is attained under the environment, and 5% CO₂ is preferably allowed to flow. The culturing period is not restricted as long as a necessary number of the cells are induced therewith, and usually 3 days to 2 weeks. As for the apparatuses used for separation and culturing of the cells, appropriate apparatuses, preferably those whose safety upon application to medical uses have been confirmed and whose operations are stable and simple, may be employed. In particular, as for the cell-culturing apparatus, not only a general vessel such as a Petri dish, flask or bottle, but also a layer type vessel, multistage vessel, roller bottle, spinner type bottle, bag type culturing vessel, hollow fiber column or the like may be used.

[0068]

The method per se to be used for bringing the above-described polypeptide into contact with the antigen presenting cells in vitro may be carried out by a well-known method. For example, it may be carried out by culturing the antigen-presenting cells in a culture medium containing the above-described polypeptide. The concentration of the peptide in the medium is not restricted, and usually about 1 to 100 µg/ml, preferably about 5 to 20 µg/ml. The cell density during the culture is not restricted and usually about 10³ to 10⁷ cells/ml, preferably about 5×10⁴ to 5×10⁶ cells/ml. The culture may be carried out according to a conventional method at 37°C under the atmosphere of 5% CO₂. The maximum length of the peptide which can be presented on the surface of the antigen-presenting cells is usually about 30 amino acid residues. Therefore, in cases where the antigen-presenting cells are brought into contact with the polypeptide in vitro, the polypeptide may be prepared such that its length is not more than about 30 amino acid residues, although the length is not restricted.

[0069]

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

10 [0070]

By bringing the thus prepared antigen-presenting cells having the complex between the above-described polypeptide and the MHC molecule into contact with T cells in vitro, cytotoxic T cells specific to the polypeptide can be induced and allowed to proliferate. This may be carried out by coculturing the above-described antigen-presenting cells and T cells in a liquid medium. For example, it may be attained by suspending the antigen-presenting cells in a liquid medium, placing the suspension in vessels such as wells of a microplate, adding T cells thereto and then culturing the cells. The mixing ratio of the antigen-presenting cells with respect to the T cells in the coculture is not restricted, and is usually about 1:1 to 1:100, preferably about 1:5 to 1:20 in terms of the ratio between the numbers of the cells. The density of the antigen-presenting cells to be suspended in the liquid medium is not restricted, and is usually about 100 to 10,000,000 cells/ml, preferably about 10,000 to 1,000,000 cells/ml. The coculture is preferably carried out in accordance with a conventional method at 37°C under the atmosphere of 5% CO₂. The culturing period is not restricted, and is usually 2 days to 3 weeks, preferably about 4 days to 2 weeks. The coculture is preferably carried out in the presence of one or more interleukins such as IL-2, IL-6, IL-7 and/or IL-12. In such cases, the

concentration of IL-2 or IL-7 is usually about 5 to 20 U/ml, the concentration of IL-6 is usually about 500 to 2000 U/ml, and the concentration of IL-12 is usually about 5 to 20 ng/ml, but the concentrations of the interleukins are not restricted thereto. The above coculture may be repeated once to several times with addition of fresh antigen-presenting cells. For example, the operation of discarding the culture supernatant after the coculture and adding a fresh suspension of antigen-presenting cells to further conduct the coculture may be repeated once to several times. The conditions of each coculture may be the same as described above.

[0071]

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

[0072]

As described in the Examples below, the gene encoding PDS5A is expressed specifically in breast cancer cells, breast cancer tissues, brain tumor cells, brain tumor tissues, esophagus cancer cells, esophagus cancer tissues, lung cancer cells, lung cancer tissues, renal cancer cells, renal cancer tissues, colon cancer cells, colon cancer tissues, perianal adenocarcinoma tissues, perianal adenocarcinoma cells, neuroblastoma cells and leukemia cells. Therefore, it is thought that, in these cancer species, a significantly larger amount of PDS5A exists than in normal cells. When cytotoxic T cells prepared as described above are administered to a living body while a part of PDS5A existing in cancer cells is presented by MHC molecules on the surface of the cancer cells, the cytotoxic T cells can damage the cancer cells using the presented polypeptide as a marker. Since antigen-presenting cells presenting the above-described polypeptide can induce, and allow proliferation of, cytotoxic T cells specific to the polypeptide also in vivo, cancer cells can be damaged also by

administering the antigen-presenting cells to a living body. That is, the cytotoxic T cells and the antigen-presenting cells prepared using the polypeptide are also effective as therapeutic and/or prophylactic agents for cancer, similarly to the immunity-inducing agent of the present invention.

5 [0073]

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

10 [0074]

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

20 [0075]

Also by expressing a polynucleotide encoding any of the polypeptides (a) to (c) in the body of the subject animal, antibody production and cytotoxic T cells can be induced in the living body, and an effect comparable to that obtained in the case of administration of the polypeptide can be obtained. That is, the immunity-inducing

agent of the present invention may be one comprising as an effective ingredient a recombinant vector having a polynucleotide encoding any of the polynucleotides (a) to (c), which recombinant vector is capable of expressing the polypeptide in a living body. Such a recombinant vector capable of expressing an antigenic polypeptide as shown in the later-mentioned Examples is also called a gene vaccine.

[0076]

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

[0077]

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

[0078]

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

especially preferred.

[0079]

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

[0080]

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

[0081]

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

liposome may be formulated into a liposome preparation such as a suspension, frozen preparation or centrifugally concentrated frozen preparation.

[0082]

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

[0083]

15 Further, since the polypeptide used in the present invention is expressed specifically in cancer, the polypeptide specifically reacts only with the serum in a cancer-bearing living body, so that the polypeptide of the present invention is used also for detection of cancer.

[0084]

20 In the above-described method for detecting cancer, a sample separated from a living body is used to measure expression of a polypeptide having any one of the amino acid sequences shown in SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, or a polypeptide as a homologous factor thereof, having a sequence identity of not less than 90%, preferably not less than 95%, more preferably not less than 98%, still more
25 preferably not less than 99% or not less than 99.5% to the polypeptide. Examples of the method for measuring the expression of the polypeptide using the sample includes a method in which an antibody against the polypeptide, which antibody is

contained in the sample, is measured by immunoassay (Method 1); a method in which the polypeptide per se contained in the sample is measured by immunoassay (Method 2); and a method in which mRNA contained in the sample and encoding the polypeptide is measured (Method 3). In the method of the present invention, the expression of the polypeptide may be measured by any of these methods. In the present invention, the term "measurement" includes detection, quantification and semi-quantification.

[0085]

Here, PDS5A is a polypeptide identified, by the SEREX method using a canine breast cancer-derived cDNA library and serum obtained from the same patient dog, as a polypeptide that binds to an antibody specifically existing in the serum derived from the tumor-bearing dog (cancer-specific antibody) (see Example 1). That is, in the living body of the tumor-bearing dog, an antibody against PDS5A is specifically induced. Therefore, by measuring the antibody against PDS5A in the living body of the tumor-bearing dog, a cancer expressing PDS5A can also be detected. Further, also by measuring PDS5A as an antigen by Method 2, the canine cancer can be detected. Further, since, as described in the later-mentioned Examples, mRNA encoding the antigen polypeptide is expressed at significantly higher levels in cancer cells and cancer tissues, especially in breast cancer cells, breast cancer tissues, brain tumor cells, brain tumor tissues, esophagus cancer cells, esophagus cancer tissues, lung cancer cells, lung cancer tissues, renal cancer cells, renal cancer tissues, colon cancer cells, colon cancer tissues, perianal adenocarcinoma cells, perianal adenocarcinoma tissues, neuroblastoma cells and leukemia cells, compared to the normal tissues (see Example 1), the canine cancer can be detected also by measuring the mRNA.

[0086]

In Method 1 above, measurement of the cancer-specific antibody which may

exist in the sample can be easily carried out by immunoassay using an antigenic substance which undergoes antigen-antibody reaction with the antibody. The immunoassay per se is a conventional well-known method as explained in detail below. Examples of the antigenic substance which may be used in the immunoassay include the polypeptides (a) to (c). Since antibodies have cross-reactivity, even a molecule other than the antigenic substance corresponding to the original immunogen may be bound to an antibody induced against the immunogen by antigen-antibody reaction, as long as the molecule has a structure thereon similar to an epitope of the immunogen. For example, polypeptides having a high sequence identity therebetween often have similar epitope structures, and, in this case, the both polypeptides may have the same antigenicity. As concretely described in the Examples below, the human-derived polypeptide of SEQ ID NO:4 or 44 undergoes antigen-antibody reaction with the above-described antibody induced in the body of a cancer-bearing dog. Therefore, in Method 1 of the present invention, any mammalian homologous factor may be used as the antigen in the immunoassay.

[0087]

An antigenic substance having a complex structure and a large molecular weight, such as a protein, usually has a plurality of sites having different structures on the molecule. Therefore, against such an antigenic substance, a plurality of kinds of antibodies which recognize the respective plurality of sites are produced in a living body. That is, an antibody induced in a living body against an antigenic substance such as a protein is a polyclonal antibody, which is a mixture of a plurality of kinds of antibodies. It should be noted that, in the present invention, the term "polyclonal antibody" means antibodies which exist in serum from a living body having an antigenic substance therein and were induced in the living body against the antigenic substance.

[0088]

Measurement of the antibody in a sample may easily be carried out by immunoassay using the above-described polypeptide as an antigen. Immunoassays per se are well-known in the art, and include, when classified based on the reaction mode, the sandwich method, competition method, agglutination method, Western blotting and the like. When classified based on the label, immunoassays include radioimmunoassay, fluorescence immunoassay, enzyme immunoassay, biotin immunoassay and the like, and the immunoassay of the above-described antibody may be carried out by any of these immunoassays. Although not restricted, the sandwich ELISA and the agglutination method may be preferably applied as the method of immunoassay of the above antibody in the present invention, since the operations are simple and a large-scale apparatus is not necessary in these methods. In cases where an enzyme is used as the label of the antibody, the enzyme is not particularly restricted as long as it satisfies conditions such as a large turnover number, stability upon binding with the antibody, and specific coloring of the substrate, and examples of the enzyme which may be used include enzymes used in an ordinary enzyme immunoassay, such as peroxidase, β -galactosidase, alkaline phosphatase, glucose oxidase, acetylcholinesterase, glucose-6-phosphate dehydrogenase, and malate dehydrogenase. An enzyme inhibitor, coenzyme and/or the like may also be used. Binding of the enzyme with the antibody may be carried out by a known method using a cross-linking agent such as a maleimide compound. As a substrate, a known substance may be used depending on the type of the enzyme to be used. For example, in cases where peroxidase is used as the enzyme, 3,3',5,5'-tetramethylbenzidine may be used; and in cases where alkaline phosphatase is used as the enzyme, para-nitrophenol or the like may be used. As a radioisotope, one used in an ordinary radioimmunoassay, such as ^{125}I or ^3H may be used. As a fluorescent dye, one used in an ordinary fluorescent antibody technique, such as fluorescein isothiocyanate (FITC), tetramethylrhodamine isothiocyanate (TRITC) or

the like may be used.

[0089]

These immunoassays per se are well-known in the art and do not need to be explained in the present specification. Briefly, in a sandwich immunoassay, for example, the above-mentioned polypeptide used as an antigen is immobilized on a solid phase and then reacted with a sample such as a serum. After washing the solid phase, the resultant is reacted with an appropriate secondary antibody. After washing the solid phase, the secondary antibody bound to the solid phase is measured. This method is preferred as an embodiment of the method of the present invention for detecting cancer since, in this method, immobilization of the antigen polypeptide to the solid phase enables simple removal of unbound secondary antibodies. As the secondary antibody, an anti-dog IgG antibody may be used in cases where, for example, the sample is derived from a dog. By preliminarily labeling the secondary antibody with a labeling substance exemplified above, the secondary antibody bound to the solid phase can be measured. The thus measured amount of the secondary antibody corresponds to the amount of the above-mentioned antibody in the serum sample. In cases where an enzyme is used as the labeling substance, the amount of the antibody may be measured by adding a substrate which develops a color upon decomposition by an enzymatic activity, and then optically measuring the amount of decomposition of the substrate. In cases where a radioisotope is used as the labeling substance, the amount of radiation emitted from the radioisotope may be measured with a scintillation counter or the like.

[0090]

In Method 2 of the present invention, the polypeptide of SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 or a homologous factor thereof, which may be contained in a sample obtained from a living body is measured. As mentioned above, the amount of a cancer-specific antibody which undergoes antigen-antibody reaction with the

polypeptide of SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 or a homologous factor thereof is significantly larger in cancer patients, and this indicates that the amount of production of the polypeptide or a homologous factor thereof, which corresponds to an antigen of the cancer-specific antibody, is significantly larger in the cancer patients. Therefore, cancer in a living body can be detected also by measuring the polypeptide of SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 or a homologous factor thereof similarly to Method 1 described above.

[0091]

The polypeptide in a sample can be easily measured by a well-known immunoassay. More particularly, for example, by preparing an antibody or an antigen-binding fragment thereof which undergoes antigen-antibody reaction with the polypeptide shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 and using this in an immunoassay, the polypeptide having the sequence shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 or a homologous factor thereof which may exist in the sample can be measured. The immunoassay per se is a well-known conventional method as described above.

[0092]

The term "antigen-binding fragment" herein means an antigen fragment such as the Fab fragment or F(ab')₂ fragment contained in the antibody molecule, which has a binding capacity to an antigen. The antibody may be either a polyclonal antibody or monoclonal, and a monoclonal antibody is preferred in an immunoassay and the like because a high reproducibility can be obtained therewith. The methods of preparation of a polyclonal antibody and a monoclonal antibody using a polypeptide as an immunogen are well known, and can be easily carried out by conventional methods. For example, antibodies against a polypeptide can be induced by immunizing an animal with, as an immunogen, the polypeptide conjugated to a carrier protein such as keyhole limpet hemocyanin (KLH) or casein,

together with an adjuvant. Antibody-producing cells such as spleen cells or lymphocytes are then collected from the immunized animal and fused with myeloma cells to prepare hybridomas. Among the hybridomas, one producing an antibody which binds to the polypeptide shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44, or a homologous factor thereof is selected and proliferated, and then a monoclonal antibody whose corresponding antigen is the above-mentioned protein can be obtained from the culture supernatant. The above-described method is a conventional well-known method.

[0093]

10 In Method 3 of the present invention, mRNA which may be contained in a sample obtained from a living body and encodes PDS5A is measured. As concretely shown in the Examples below, mRNA encoding PDS5A is significantly highly expressed in tissues and cells of cancer, breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, perianal adenocarcinoma, neuroblastoma and leukemia. Therefore, also by measuring the mRNA in the sample, cancer in the living body can be detected.

[0094]

20 In the detection method of the present invention, whether or not a subject living body is suffering from cancer is judged based on the expression level of the polypeptide measured as described above. Although the cancer detection may be attained simply by measuring expression of the polypeptide in the subject living body, it is preferred, from the viewpoint of enhancement of the detection accuracy, to obtain a normal reference value by investigating the expression level of the polypeptide (the amount of the antibody, polypeptide or mRNA) in one or more samples from healthy individuals, followed by comparison of the measured value in the subject living body with the normal reference value. In cases where a higher detection accuracy is required, a cancer reference value may be obtained by

investigating the expression level of the polypeptide in samples obtained from many patients known to be suffering from cancer, followed by comparison of the measured value in the subject living body both with the normal reference value and with the cancer reference value. The reference values may be determined by, for example, digitizing the expression level of the polypeptide in each sample and calculating the mean value. The normal reference value and the cancer reference value may be preliminarily determined by investigating the expression level of the polypeptide in many healthy individuals and cancer patients. Thus, in cases where comparison with the reference value(s) is carried out in the method of the present invention, a preliminarily determined reference value(s) may be used.

[0095]

The detection method of the present invention may be used in combination with detection with another cancer antigen or cancer marker. By this, the accuracy of detection of cancer can be further increased.

[0096]

By the detection method of the present invention, cancers in a living body can be detected. By the method of the present invention, even an invisible small cancer or a cancer which exists in a deep part of a body can be detected, and thus the method is useful for early detection of cancers. Further, by applying the detection method of the present invention to patients in the follow-up period after cancer therapy, a recurrent cancer, if any, can be detected at an early stage.

[0097]

In a tumor-bearing living body, as the number of cancer cells expressing the specific polypeptide to be measured in the present invention increases, the amounts of accumulation of the polypeptide and the mRNA encoding it in the living body increase, leading to increased production of antibodies against the polypeptide in the serum. On the other hand, as the number of cancer cells decreases, the amounts of

accumulation of the polypeptide and the mRNA encoding it in the living body decrease, leading to decrease in antibodies against the polypeptide in the serum. Thus, in cases where the expression level of the specific polypeptide is high, it can be determined that tumor growth and/or metastasis of cancer occurred, that is, the stage of progression of cancer is advanced.

[0098]

Further, as shown in the Examples below, when compared between the same kind of tumors, a malignant one produces a significantly higher amount of the antibodies than a benign one. Therefore, in cases where the expression level of the specific polypeptides is high, it can be determined that the grade of cancer malignancy is high. That is, the grade of cancer malignancy can also be detected by the method of the present invention.

[0099]

Furthermore, the effect of a cancer therapy can be monitored based on increase or decrease of the expression level of the specific polypeptide. Therefore, by observing the expression level of the above-mentioned polypeptide in an individual during or after a cancer therapy, one can obtain a clue(s) to know the effect of an anticancer drug, presence/absence of a residual tumor after extirpation of the tumor, and/or, even during the follow-up, metastasis and/or recurrence, as early as possible. In cases where a therapy is/was appropriate, the expression level of the polypeptide becomes lower than that in the patient in the tumor-bearing state before the therapy, and therefore the effect of the therapy that was (or is being) provided for the living body can be judged to have been (or to be) excellent. In cases where the expression level of the polypeptide increased or is maintained, or in cases where the expression level once decreased and then increased again, the therapeutic effect can be judged to be insufficient, and this observation can be a useful basis for selection of a therapeutic method, such as use of another therapeutic method or alteration of the

dose of an anti-cancer agent.

[0100]

Preferred examples of the cancer as the subject of the method for detecting cancer of the present invention include cancers expressing PDS5A, such as breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, 5 perianal adenocarcinoma, neuroblastoma and leukemia. The living body as the subject of the method of the present invention is preferably a mammal, more preferably human, dog or cat.

[0101]

10 The sample to be provided for the method of the present invention include body fluids such as blood, serum, plasma, ascites and pleural effusion, and tissues and cells. Particularly, serum, plasma, ascites and pleural effusion may be preferably used in Method 1 and Method 2 above. A tissue sample and cell sample are preferred in the case of Method 3 above in which mRNA is measured.

15 [0102]

The polypeptide used as the antigen for the immunoassay in Method 1 may be provided as a reagent for cancer detection. The reagent may consist essentially of the above-mentioned polypeptide, or may contain, for example, various additives useful for stabilizing the polypeptide, and/or the like. The reagent may be provided 20 also in a state where it is immobilized on a solid phase such as a plate or membrane.

[0103]

When the polypeptide shown in SEQ ID NO:2, 4, 6, 8, 10, 12 or 44 or a homologous factor thereof is to be immunoassayed in Method 2, an antibody or an antigen-binding fragment thereof which undergoes antigen-antibody reaction with the polypeptide or a homologous factor thereof may also be provided as a reagent for 25 cancer detection. Also in this case, the reagent for cancer detection may consist essentially of the antibody or antigen-binding fragment, or may contain, for example,

various additives useful for stabilizing the antibody or antigen-binding fragment, and/or the like. The antibody or antigen-binding fragment may also be in a state where a metal such as manganese or iron is bound thereto. Administration of such a metal-bound antibody or antigen-binding fragment into a living body causes higher accumulation of the antibody or antigen-binding fragment at locations where the antigen protein exists in a larger amount, so that measurement of the metal by MRI or the like enables detection of existence of cancer cells that produces the antigen protein.

[0104]

Furthermore, the above-described polynucleotide for cancer detection to be used for measuring mRNA in Method 3 may also be provided as a reagent for cancer detection. Also in this case, the reagent for cancer detection may consist essentially of the polynucleotide, or may contain, for example, various additives useful for stabilizing the polynucleotide, and/or the like. The polynucleotide for cancer detection contained in the reagent is preferably a primer or a probe.

EXAMPLES

[0105]

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

[0106]

Example 1: Obtaining Novel Cancer Antigen Protein by SEREX Method

(1) Preparation of cDNA Library

Total RNA was extracted from a breast cancer tissue of a tumor-bearing dog by the Acid guanidium-Phenol-Chloroform method, and poly(A) RNA was purified using Oligotex-dT30 mRNA purification Kit (manufactured by Takara Shuzo Co., Ltd.) in accordance with the protocol attached to the kit.

[0107]

Using the obtained mRNA (5 μ g), a cDNA phage library was synthesized. For the preparation of the cDNA phage library, cDNA Synthesis Kit, ZAP-cDNA Synthesis Kit, and ZAP-cDNA Gigapack III Gold Cloning Kit (manufactured by STRATAGENE) were used in accordance with the protocols attached to the kits.

5 The size of the prepared cDNA phage library was 1×10^6 pfu/ml.

[0108]

(2) Screening of cDNA Library with Serum

Using the prepared cDNA phage library, immunoscreening was carried out. More particularly, the host *E. coli* (XL1-Blue MRF') was infected with the library
10 such that 2340 clones appear on an NZY agarose plate having a size of $\Phi 90 \times 15$ mm, and cultured at 42°C for 3 to 4 hours to allow the phage to form plaques. The plate was covered with a nitrocellulose membrane (Hybond C Extra: manufactured by GE Healthcare Bio-Science) impregnated with IPTG (isopropyl- β -D-thiogalactoside) at 37°C for 4 hours to allow induction and expression of proteins, which were thus
15 transferred to the membrane. Subsequently, the membrane was recovered and soaked in TBS (10 mM Tris-HCl, 150 mM NaCl; pH 7.5) containing 0.5% non-fat dry milk, followed by shaking it at 4°C overnight to suppress non-specific reactions. This filter was then allowed to react with 500-fold diluted canine patient serum at room temperature for 2 to 3 hours.

20 [0109]

As the above-described canine patient serum, serum collected from a canine patient suffering from perianal tumor was used. The serum was stored at -80°C and pretreated immediately before use. The method of the pretreatment of the serum was as follows. That is, the host *E. coli* (XL1-Blue MRF') was infected with λ ZAP
25 Express phage to which no foreign gene was inserted, and then cultured on NZY plate medium at 37°C overnight. Subsequently, 0.2 M NaHCO₃ buffer (pH 8.3) containing 0.5 M NaCl was added to the plate, and the plate was left to stand at 4°C

for 15 hours, followed by collecting the supernatant as an *E. coli*/phage extract. Thereafter, the collected *E. coli*/phage extract was allowed to flow through an NHS column (manufactured by GE Healthcare Bio-Science) to immobilize proteins derived from the *E. coli*/phage thereon. The serum from the canine patient was
5 allowed to flow through and react with this protein-immobilized column to remove antibodies adsorbed to *E. coli* and/or the phage. The serum fraction that passed through the column was 500-fold diluted with TBS containing 0.5% non-fat dry milk, and the resulting diluent was used as the material for the immunoscreening.

[0110]

10 The membrane on which the thus treated serum and the above-described fusion protein were blotted was washed 4 times with TBS-T (0.05% Tween 20/TBS), and allowed to react with goat anti-dog IgG (Goat anti Dog IgG-h+I HRP conjugated: manufactured by BETHYL Laboratories) 5,000-fold diluted with TBS containing 0.5% non-fat dry milk as a secondary antibody at room temperature for 1 hour,
15 followed by detection by the enzyme coloring reaction using the NBT/BCIP reaction solution (manufactured by Roche). Colonies at positions where a positive coloring reaction was observed were recovered from the NZY agarose plate having a size of $\Phi 90 \times 15$ mm, and dissolved in 500 μ l of SM buffer (100 mM NaCl, 10 mM MgClSO_4 , 50 mM Tris-HCl, 0.01% gelatin; pH 7.5). The screening was repeated as
20 a second and third screening in the same manner as described above until a single coloring reaction-positive colony was obtained, thereby isolating one positive clone after screening of 30940 phage clones reactive with IgG in the serum.

[0111]

(3) Sequence Homology Search of Isolated Antigen Gene

25 To subject the single positive clone isolated by the above-described method to a base sequence analysis, an operation of conversion of the phage vector to a plasmid vector was carried out. More particularly, 200 μ l of a solution prepared such that

the host *E. coli* (XL1-Blue MRF') was contained at an absorbance OD₆₀₀ of 1.0 was mixed with 100 µl of a purified phage solution and further with 1 µl of ExAssist helper phage (manufactured by STRATAGENE), and the reaction was allowed to proceed at 37°C for 15 minutes. To the reaction mixture, 3 ml of LB medium was added, and the resulting mixture was cultured at 37°C for 2.5 to 3 hours, followed by immediate incubation in a water bath at 70°C for 20 minutes. The mixture was then centrifuged at 4°C at 1,000 ×g for 15 minutes, and the supernatant was recovered as a phagemid solution. Subsequently, 200 µl of a solution prepared such that the phagemid host *E. coli* (SOLR) was contained at an absorbance OD₆₀₀ of 1.0 was mixed with 10 µl of a purified phage solution, and the reaction was allowed to proceed at 37°C for 15 minutes. Thereafter, 50 µl of the reaction mixture was plated on LB agar medium supplemented with ampicillin (final concentration: 50 µg/ml), and cultured at 37°C overnight. A single colony of transformed SOLR was recovered and cultured in LB medium supplemented with ampicillin (final concentration: 50 µg/ml) at 37°C, followed by purification of plasmid DNA having the insert of interest using QIAGEN plasmid Miniprep Kit (manufactured by Qiagen).

[0112]

The purified plasmid was subjected to analysis of the full-length sequence of the insert by the primer walking method using the T3 primer described in SEQ ID NO:13 and the T7 primer described in SEQ ID NO:14. By this sequence analysis, the gene sequence described in SEQ ID NO:1 was obtained. Using the base sequence and the amino acid sequence of this gene, homology search against known genes was carried out using a sequence homology search program BLAST (<http://www.ncbi.nlm.nih.gov/BLAST/>). As a result, it was revealed that the obtained gene is the PDS5A gene. Human PDS5A, which is a human homologous factor of canine PDS5A, had a sequence identity of 94% in terms of the base sequence and 99% in terms of the amino acid sequence; murine PDS5A, which is a

murine homologous factor, had a sequence identity of 91% in terms of the base sequence and 99% in terms of the amino acid sequence; bovine PDS5A, which is a bovine homologous factor, had a sequence identity of 95% in terms of the base sequence and 99% in terms of the amino acid sequence; equine PDS5A, which is a equine homologous factor, had a sequence identity of 96% in terms of the base sequence and 99% in terms of the amino acid sequence; and chicken PDS5A, which is a chicken homologous factor, had a sequence identity of 83% in terms of the base sequence and 98% in terms of the amino acid sequence. In terms of human PDS5A, the base sequence is shown in SEQ ID NOs:3 and 43, and the amino acid sequence is shown in SEQ ID NOs:4 and 44; in terms of murine PDS5A, the base sequence is shown in SEQ ID NO:5, and the amino acid sequence is shown in SEQ ID NO:6; in terms of bovine PDS5A, the base sequence is shown in SEQ ID NO:7, and the amino acid sequence is shown in SEQ ID NO:8; in terms of equine PDS5A, the base sequence is shown in SEQ ID NO:9, and the amino acid sequence is shown in SEQ ID NO:10; and in terms of chicken PDS5A, the base sequence is shown in SEQ ID NO:11, and the amino acid sequence is shown in SEQ ID NO:12.

[0113]

(4) Analysis of Expression in Various Tissues

Expression of the genes obtained by the above method in canine, human and murine normal tissues and various cell lines were investigated by the RT-PCR (Reverse Transcription-PCR) method. The reverse transcription reaction was carried out as follows. That is, from 50 to 100 mg of each tissue or 5×10^6 to 10×10^6 cells of each cell line, total RNA was extracted using the TRIZOL reagent (manufactured by INVITROGEN) according to the protocol described in the attached instructions. Using this total RNA, cDNA was synthesized with the Superscript First-Strand Synthesis System for RT-PCR (manufactured by INVITROGEN) according to the protocol described in the attached instructions. As the cDNAs of

human normal tissues (brain, hippocampus, testis, colon and placenta), Gene Pool cDNA (manufactured by INVITROGEN), QUICK-Clone cDNA (manufactured by CLONETECH) and Large-Insert cDNA Library (manufactured by CLONETECH) were used. The PCR reaction was carried out using gene-specific primers (the canine primers described in SEQ ID NOs:15 and 16, the human primers described in SEQ ID NOs:17 and 18, and the murine primers described in SEQ ID NOs:19 and 20) as described below. That is, reagents and an attached buffer were mixed such that 0.25 μ l of the sample prepared by the reverse transcription reaction, 2 μ M each of the above primers, 0.2 mM each of dNTPs, and 0.65 U ExTaq polymerase (manufactured by Takara Shuzo Co., Ltd.) were contained in a total volume of 25 μ l, and the reaction was carried out by repeating 30 times the cycle of 94°C for 30 seconds, 55°C for 30 seconds and 72°C for 1 minute using a Thermal Cycler (manufactured by BIO RAD). As a control for comparison, primers specific to GAPDH (the canine and human GAPDH primers are shown in SEQ ID NOs:21 and 22; and the murine GAPDH primers are shown in SEQ ID NOs:23 and 24) were used at the same time. As a result, as shown in Fig. 1, in terms of the canine PDS5A gene, expression was not observed in most of the healthy canine tissues, while strong expression was observed in the canine tumor tissues. Also in terms of the human and murine PDS5A genes, expression was not observed in most of the healthy human and murine tissues, while expression was detected in most of the cancer cell lines (Figs. 2 and 3), as in the case of the canine PDS5A gene.

[0114]

Example 2: Analysis of Cancer Antigenicity and Evaluation of Pharmacological Effect of PDS5A in Living Body

(1) Preparation of Recombinant Vector That Expresses PDS5A in Living Body

Based on the base sequence of SEQ ID NO:5, a recombinant vector that expresses PDS5A in a living body was prepared. Reagents and an attached buffer

were mixed together such that 1 μ l of the cDNA prepared from the murine cancer cell line N2a (purchased from ATCC), which showed expression in Example 1, 0.4 μ M each of two kinds of primers having the *Not*I and *Xho*I restriction sites (shown in SEQ ID NOs:25 and 26), 0.2 mM dNTP and 1.25 U PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) were contained in a total volume of 50 μ l, and PCR was carried out by repeating 30 times the cycle of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 4 minute using a Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those for amplification of the region encoding the full-length of the amino acid sequence shown in SEQ ID NO:5. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 4000 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0115]

The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and the plasmid was then recovered. The amplified gene fragment was confirmed to have the same sequence as that of interest by sequencing. The plasmid having the same sequence as that of interest was treated with restriction enzymes *Not*I and *Xho*I, and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into a mammalian expression vector PCDNA3.1 (manufactured by Invitrogen) that had been treated with restriction enzymes *Not*I and *Xho*I. Use of this vector enables production of the PDS5A protein in mammalian cells.

[0116]

To 100 μ g of the thus prepared plasmid DNA, 50 μ g of gold particles (manufactured by Bio Rad), 100 μ l spermidine (manufactured by SIGMA) and 100 μ l of 1 M CaCl_2 (manufactured by SIGMA) were added, and the resulting mixture was

stirred by vortexing, followed by leaving the mixture to stand for 10 minutes at room temperature (the resulting particles are hereinafter referred to as gold-DNA particles). The mixture was then centrifuged at 3000 rpm for 1 minute and the supernatant was discarded, followed by rinsing the precipitate 3 times with 100% ethanol
5 (manufactured by WAKO). To the gold-DNA particles, 6 ml of 100% ethanol was added, and the resulting mixture was sufficiently stirred by vortexing, followed by pouring the gold-DNA particles into Tefzel Tubing (manufactured by Bio Rad) and allowing the particles to precipitate on the wall surface. The ethanol in the Tefzel Tubing to which the gold-DNA particles are attached was dried in the air, and the
10 tube was cut into pieces having a length appropriate for a gene gun.

[0117]

(2) Anti-tumor Effect of PDS5A by DNA Vaccine Method

Each of a murine neuroblastoma cell line N2a and a colon cancer cell line CT26 were subcutaneously transplanted to 10 individuals of A/J mice (7 weeks old, male, purchased from Japan SLC) and Balb/c mice (7 weeks old, male, purchased
15 from Japan SLC) in an amount of 1×10^6 cells. The above prepared tube was fixed in a gene gun, and a pressure of 400 psi was applied using pure helium gas to perform percutaneous administration of the DNA vaccine to the abdominal cavity of each mouse whose hair had been shaved, which administration was repeated a total
20 of 3 times at intervals of 7 days (this corresponds to 2 μ g/individual in terms of the dose of the inoculated amount of the plasmid DNA) to evaluate the anti-tumor effect (therapeutic model). Further, in a similar manner, the DNA vaccine was subcutaneously administered to each of 10 individuals of A/J mice and Balb/c mice a total of 3 times at intervals of 7 days, and N2a cells or CT26 cells were then
25 transplanted to each mouse to evaluate the anti-tumor effect (prophylactic model). As a control, a plasmid DNA to which the PDS5A gene was not inserted was administered to 10 individuals in each model.

[0118]

The anti-tumor effect was evaluated based on the size of the tumor (major axis $\times$ minor axis² / 2) and the ratio of living mice. The results are shown in Figs. 4 to 11. As a result of this study, in the therapeutic model using the neuroblastoma cell line, the size of the tumor on Day 41 was 569 mm³ and 109 mm³ in the control group and the PDS5A plasmid-administered group, respectively, indicating significant reduction of the tumor in the PDS5A plasmid-administered group (Fig. 4). Similarly, in the prophylactic model using the neuroblastoma cell line, the size of the tumor on Day 43 was 476 mm³ and 0 mm³ in the control group and the PDS5A plasmid-administered group, respectively, indicating complete regression of the tumor in the PDS5A plasmid-administered group (Fig. 5). Further, in the therapeutic model using the colon cancer cell line, the size of the tumor on Day 41 was 589 mm³ and 189 mm³ in the control group and the PDS5A plasmid-administered group, respectively, indicating significant reduction of the tumor in the PDS5A plasmid-administered group (Fig. 8). Further, in the prophylactic model using the colon cancer cell line, the size of the tumor on Day 43 was 397 mm³ and 43 mm³ in the control group and the PDS5A plasmid-administered group, respectively, indicating significant reduction of the tumor in the PDS5A plasmid-administered group (Fig. 9). Based on observation of the process of survival in the both models using the neuroblastoma cell line, while all the cases in the control group died by Day 84 after the administration, 60% of the mice were alive at that time in the PDS5A plasmid-administered group (Fig. 6). Further, in the prophylactic model, while all the cases in the control group died by Day 90 after the administration, all the mice were alive at that time in the PDS5A plasmid-administered group (Fig. 7). Further, based on observation of the process of survival in the both models using the colon cancer cell line, while all the cases in the control group died by Day 84 after the administration, 40% of the mice were alive at that time in the PDS5A plasmid-

administered group (Fig. 10). Further, in the prophylactic model, while all the cases in the control group died by Day 90 after the administration, 80% of the mice were alive at that time in the PDS5A plasmid-administered group (Fig. 11).

[0119]

5 In the above results, a significantly higher anti-tumor effect was observed in the PDS5A-plasmid administered group than in the control group, and, by this observation, it was revealed that PDS5A is a cancer antigen having a strong cancer antigenicity and effective for therapy and prophylaxis of cancer.

[0120]

10 Example 3: Induction of Peptide Epitope-reactive CD8-positive T Cells

For prediction of an HLA-A0201-binding motif in the amino acid sequence of the human PDS5A protein, a computer-based prediction program using the known BIMAS software (available at http://bimas.dcrt.nih.gov/molbio/hla_bind/) was used to analyze the amino acid sequences shown in SEQ ID NOs:4 and 44, and thereby the
15 polypeptides shown in SEQ ID NOs:27 to 35, which were expected to be capable of binding to the HLA class I molecule, were selected.

[0121]

From an HLA-A0201-positive healthy individual, peripheral blood was separated, and the peripheral blood was overlaid on Lymphocyte separation medium
20 (Organon Teknika, Durham, NC), followed by centrifuging the resultant at 1,500 rpm at room temperature for 20 minutes. A fraction containing peripheral blood mononuclear cells (PBMCs) was recovered and washed 3 times in a cold phosphate buffer, to obtain PBMCs. The obtained PBMCs were suspended in 20 ml of AIM-V medium (Life Technologies, Inc., Grand Island, NY, USA), and the cells were
25 allowed to attach to a culture flask (Falcon) at 37°C under 5% CO₂ for 2 hours. Unattached cells were used for preparation of T cells, and attached cells were used for preparation of dendritic cells.

[0122]

The attached cells were cultured in AIM-V medium in the presence of IL-4 (1000 U/ml) and GM-CSF (1000 U/ml). The medium was replaced 6 days later with AIM-V medium supplemented with IL-4 (1000 U/ml), GM-CSF (1000 U/ml),
5 IL-6 (1000 U/ml, Genzyme, Cambridge, MA), IL-1 β (10 ng/ml, Genzyme, Cambridge, MA) and TNF- α (10 ng/ml, Genzyme, Cambridge, MA), and the culture was carried out for additional 2 days to obtain a population of unattached cells, which were employed as the dendritic cells.

[0123]

10 The prepared dendritic cells were suspended in AIM-V medium at a cell density of 1×10^6 cells/ml, and each of the selected polypeptides was added at a concentration of 10 μ g/ml to the suspension. Using a 96-well plate, the cells were cultured at 37°C under 5% CO₂ for 4 hours. After the culture, X-ray irradiation (3000 rad) was carried out, and the cells were washed with AIM-V medium,
15 followed by being suspended in AIM-V medium supplemented with 10% human AB serum (Nabi, Miami, FL), IL-6 (1000 U/ml) and IL-12 (10 ng/ml, Genzyme, Cambridge, MA). The cells were placed in a 24-well plate in an amount of 1×10^5 cells/well. Further, the prepared T cell population was added to each well in an amount of 1×10^6 cells, and cultured at 37°C under 5% CO₂. Each culture
20 supernatant was discarded 7 days later, and dendritic cells obtained in the same manner as described above by treatment with each polypeptide and the subsequent X-ray irradiation were suspended in AIM-V medium supplemented with 10% human AB serum (Nabi, Miami, FL), IL-7 (10 U/ml, Genzyme, Cambridge, MA) and IL-2 (10 U/ml, Genzyme, Cambridge, MA) (cell density, 1×10^5 cells/ml), which
25 suspension was then added to the 24-well plate in an amount of 1×10^5 cells/well, followed by further culturing the cells. The same operation was repeated 4 to 6 times at intervals of 7 days, and stimulated T cells were then recovered, followed by

confirmation of induction of CD8-positive T cells by flow cytometry.

[0124]

Example 4: Determination of Cytotoxic T Cell Antigen Epitope in PDS5A That Stimulates HLA-A0201-positive CD8-positive T Cells

5 Among the induced T cells in the respective wells, growth of T cells stimulated by each of the polypeptides of SEQ ID NOs:27 to 35 was confirmed by counting of the cell number under the microscope. In order to investigate the specificity of the respective T cells, whose growth was confirmed, to each polypeptide used for pulsing, 5×10^3 T cells were added with respect to 5×10^4 T2
10 cells expressing the HLA-A0201 molecule (Salter RD et al., Immunogenetics, 21: 235-246 (1985), purchased from ATCC) pulsed with the polypeptide (each polypeptide was added to AIM-V medium at a concentration of 10 μ g/ml, and the cells were cultured therein at 37°C under 5% CO₂ for 4 hours), and the cells were cultured in AIM-V medium supplemented with 10% human AB serum in a 96-well
15 plate for 24 hours. After recovering the supernatant after the culture, the amount of production of IFN- γ was measured by the ELISA method. As a result, higher production of IFN- γ was confirmed in the culture supernatants in the wells containing T2 cells pulsed with the respective polypeptides shown in SEQ ID NOs:27 to 35 compared to the culture supernatants in the wells containing T2 cells which were not
20 pulsed with a polypeptide (Fig. 12). Thus, it was revealed that each of the polypeptides of SEQ ID NOs:27 to 35 is a T cell epitope peptide having a capacity to stimulate and proliferate HLA-A0201-positive CD8-positive T cells, to induce production of IFN- γ . On the other hand, in the case where the polypeptide having the amino acid sequence shown in SEQ ID NO:36, which is outside the scope of the
25 present invention, was added to perform the above-described treatment, no production of IFN- γ could be confirmed (Fig. 12).

[0125]

Subsequently, whether or not the respective polypeptides shown in SEQ ID NOs:27 to 35, which are polypeptides to be used in the present invention, are presented on HLA-A0201 molecules on HLA-A0201-positive tumor cells expressing PDS5A, and whether or not CD8-positive cells stimulated with the polypeptides can damage HLA-A0201-positive tumor cells expressing PDS5A, were studied.

[0126]

In a 50-ml centrifuge tube, 10^5 cells of a malignant brain tumor cell line T98G, whose expression of PDS5A had been confirmed (Stein GH et al., J. Cell Physiol., 99: 43-54 (1979), purchased from ATCC), were collected, and 100 μ Ci of chromium 51 was added to the tube, followed by incubation at 37°C for 2 hours. Subsequently, the cells were washed 3 times with AIM-V medium supplemented with 10% human AB serum, and placed in a 96-well V-bottomed plate in an amount of 10^3 cells per well, followed by further addition, to each well, of 10^5 , 5×10^4 , 2.5×10^4 or 1.25×10^4 HLA-A0201-positive CD8-positive T cells suspended in AIM-V medium supplemented with 10% human AB serum, which cells were stimulated with the respective polypeptides shown in SEQ ID NOs:27 to 35. The cells were then cultured at 37°C under 5% CO₂ for 4 hours. Thereafter, the amount of chromium 51 released from damaged tumor cells into the culture supernatant was measured, and thereby the cytotoxic activity of the CD8-positive T cells stimulated with each of the polypeptides shown in SEQ ID NOs:27 to 35 was calculated.

[0127]

As a result, it was revealed that the HLA-A0201-positive CD8-positive T cells stimulated with the respective polypeptides shown in SEQ ID NOs:27 to 35 have the cytotoxic activity against T98G (Fig. 13). Therefore, it became clear that the polypeptides shown in SEQ ID NOs:27 to 35, which are polypeptide to be used in the present invention, are presented on HLA-A0201 molecules on HLA-A0201-positive tumor cells expressing PDS5A, and that these polypeptides have a capacity

to induce CD8-positive cytotoxic T cells which can damage such tumor cells. On the other hand, in the case where the polypeptide having the amino acid sequence shown in SEQ ID NO:36, which is outside the scope of the present invention, was added to perform the above-described treatment, no cytotoxic activity could be observed (Fig. 13).

[0128]

The cytotoxic activity was determined by, as described above, mixing 10^5 CD8-positive T cells stimulated and induced with each of the peptides of the present invention and 10^3 cells of a malignant brain tumor cell line T98G to which chromium 51 was incorporated; culturing the resultant for 4 hours; measuring the amount of chromium 51 released into the culture medium after the culturing; and calculating the cytotoxic activity of the CD8-positive T cells against T98G according to the following equation*.

[0129]

*Equation: cytotoxic activity (%) = (Amount of chromium 51 released from T98G when CD8-positive T cells were added) / (Amount of chromium 51 released from the target cells to which 1N hydrochloric acid was added) $\times$ 100.

[0130]

Example 5: Preparation, and Evaluation of Pharmacological Effect, of Recombinant PDS5A Protein; Detection of Cancer; and Cancer Diagnosis

(1) Preparation of Recombinant PDS5A Protein

Based on the gene of SEQ ID NO:1 obtained in Example 1, a recombinant protein was prepared by the following method. Regents and an attached buffer were mixed such that 1 μ l of the vector obtained in Example 1 which was prepared from the phagemid solution and subjected to the sequence analysis, 0.4 μ M each of two kinds of primers having the *Not*I and *Xho*I restriction sites (shown in SEQ ID NOs:37 and 38), 0.2 mM dNTP and 1.25 U PrimeSTAR HS polymerase (manufactured by

Takara Shuzo Co., Ltd.) were contained in a total volume of 50 μ l, and PCR was carried out by repeating 30 times the cycle of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 4 minute using a Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those for amplification of the region encoding the full-length of the amino acid sequence shown in SEQ ID NO:2. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 4000 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0131]

10 The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and the plasmid was then recovered. The amplified gene fragment was confirmed to have the same sequence as that of interest by sequencing. The plasmid having the same sequence as that of interest was treated with restriction enzymes 15 *NotI* and *XhoI*, and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with restriction enzymes *NotI* and *XhoI*. Use of this vector enables production of a His tag-fused recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and 20 expression was induced with 1 mM IPTG, to allow expression of the protein of interest in *E. coli*.

[0132]

Further, based on the gene of SEQ ID NO:43, a recombinant protein of human PDS5A was prepared by the following method. Regents and an attached 25 buffer were mixed such that 1 μ l of the cDNA prepared in Example 1 whose expression could be confirmed with cDNAs from various tissues and cells by the RT-PCR method, 0.4 μ M each of two kinds of primers having the *NotI* and *XhoI*

restriction sites (shown in SEQ ID NOs:39 and 40), 0.2 mM dNTP and 1.25 U PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) were contained in a total volume of 50 μ l, and PCR was carried out by repeating 30 times the cycle of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 4 minute using a Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those for amplification of the region encoding the full-length of the amino acid sequence shown in SEQ ID NO:44. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 4000 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0133]

The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, and the plasmid was then recovered. The amplified gene fragment was confirmed to have the same sequence as that of interest by sequencing. The plasmid having the same sequence as that of interest was treated with restriction enzymes *NotI* and *XhoI*, and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with restriction enzymes *NotI* and *XhoI*. Use of this vector enables production of a His tag-fused recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression was induced with 1 mM IPTG, to allow expression of the protein of interest in *E. coli*.

[0134]

Further, based on the gene of SEQ ID NO:5, a recombinant protein of murine PDS5A was prepared by the following method. Regents and an attached buffer were mixed such that 1 μ l of the cDNA prepared in Example 1 whose expression

could be confirmed with cDNAs from various tissues and cells by the RT-PCR method, 0.4 μ M each of two kinds of primers having the *NotI* and *XhoI* restriction sites (shown in SEQ ID NOs:41 and 42), 0.2 mM dNTP and 1.25 U PrimeSTAR HS polymerase (manufactured by Takara Shuzo Co., Ltd.) were contained in a total volume of 50 μ l, and PCR was carried out by repeating 30 times the cycle of 98°C for 10 seconds, 55°C for 15 seconds and 72°C for 4 minute using a Thermal Cycler (manufactured by BIO RAD). The above-described two kinds of primers were those for amplification of the region encoding the full-length of the amino acid sequence shown in SEQ ID NO:6. After the PCR, the amplified DNA was subjected to electrophoresis using 1% agarose gel, and a DNA fragment of about 4000 bp was purified using QIAquick Gel Extraction Kit (manufactured by QIAGEN).

[0135]

The purified DNA fragment was ligated into a cloning vector pCR-Blunt (manufactured by Invitrogen). *E. coli* was transformed with the resulting ligation product, the plasmid was then recovered. The amplified gene fragment was confirmed to have the same sequence as that of interest by sequencing. The plasmid having the same sequence as that of interest was treated with restriction enzymes *NotI* and *XhoI*, and purified using QIAquick Gel Extraction Kit, followed by inserting the gene sequence of interest into an expression vector for *E. coli*, pET30a (manufactured by Novagen) that had been treated with restriction enzymes *NotI* and *XhoI*. Use of this vector enables production of a His tag-fused recombinant protein. *E. coli* for expression, BL21 (DE3), was transformed with this plasmid, and expression was induced with 1 mM IPTG, to allow expression of the protein of interest in *E. coli*.

[0136]

(2) Purification of PDS5A Protein

Each of the above obtained recombinant *E. coli* that expresses SEQ ID NO:2, SEQ ID NO:44 or SEQ ID NO:6 was cultured in LB medium supplemented with 100 µg/ml ampicillin at 37°C until the absorbance at 600 nm reached about 0.7, and then isopropyl-β-D-1-thiogalactopyranoside was added thereto to a final concentration of 1 mM, followed by further culturing the recombinant *E. coli* at 37°C for 4 hours. Subsequently, the bacterial cells were collected by centrifugation at 4,800 rpm for 10 minutes. The pellet of the cells was suspended in phosphate-buffered saline and further subjected to centrifugation at 4,800 rpm for 10 minutes to wash the bacterial cells.

10 [0137]

The bacterial cells were suspended in 50 mM Tris-HCl buffer (pH 8.0) and subjected to sonication on ice. The liquid obtained by the sonication of *E. coli* was centrifuged at 6000 rpm for 20 minutes, to obtain the supernatant as the soluble fraction and the precipitate as the insoluble fraction.

15 [0138]

The insoluble fraction was suspended in 50 mM Tris-HCl buffer (pH 8.0) and centrifuged at 6000 rpm for 15 minutes. This operation was repeated twice to perform an operation of removal of proteases.

[0139]

20 The residue was suspended in 50 mM Tris-HCl buffer (pH 8.0) supplemented with 6 M guanidine hydrochloride and 0.15 M sodium chloride, and left to stand at 4°C for 20 hours to denature proteins. Thereafter, the suspension was centrifuged at 6000 rpm for 30 minutes, and the obtained soluble fraction was placed in a nickel chelate column prepared by a conventional method (carrier: Chelating Sepharose (trademark) Fast Flow (GE Health Care); column volume: 5 mL; equilibration buffer: 25 50 mM Tris-HCl buffer (pH 8.0) supplemented with 6M guanidine hydrochloride and 0.15 M sodium chloride), followed by leaving the resultant to stand at 4°C overnight

to allow adsorption of the proteins to the nickel-chelated carrier. This column carrier was centrifuged at 1500 rpm for 5 minutes and the supernatant was then recovered. The column carrier was suspended in phosphate-buffered saline and refilled into the column.

5 [0140]

The fraction not adsorbed to the column was washed with 10 column volumes of 0.1 M acetate buffer (pH 4.0) supplemented with 0.5 M sodium chloride, and immediately thereafter, proteins were eluted with 0.1 M acetate buffer (pH 3.0) supplemented with 0.5 M sodium chloride, to obtain a purified fraction, which was
10 used later as a material for an administration test. The protein of interest in each eluted fraction was confirmed by Coomassie staining carried out according to a conventional method.

[0141]

The buffer of the purified preparation obtained by the above method was
15 replaced with a reaction buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM CaCl₂ (pH8.0)), and the resulting sample was subjected to cleavage of the His tag with factor Xa protease and purification of the protein of interest, using Factor Xa Cleavage Capture Kit (manufactured by Novagen) in accordance with the protocol attached to the kit. Subsequently, the buffer of 12 ml of the purified preparation
20 obtained by the above method was replaced with a physiological phosphate buffer (manufactured by Nissui Pharmaceutical) using ultrafiltration NANOSEP 10K OMEGA (manufactured by PALL), and the resulting sample was subjected to aseptic filtration through HT Tuffryn Acrodisc 0.22 μm (manufactured by PALL) and used in the experiment.

25 [0142]

(3) Anti-tumor Effect of Recombinant Murine PDS5A Protein in Tumor-bearing Mouse

The murine neuroblastoma cell line N2a was subcutaneously transplanted to A/J mice (7 weeks old, male, purchased from Japan SLC) in an amount of 1×10^6 cells. When the tumor volume reached an average of 50 to 100 mm³ (typically 7 days after the inoculation of the tumor), the mice were randomly divided into groups each of which contains 10 individuals, and subjected to evaluation of the anti-tumor effect of the recombinant murine PDS5A protein (therapeutic model). With 100 µg (0.5 ml) of the recombinant murine PDS5A protein purified as described above, 50 µg of poly I:C was mixed to prepare a therapeutic agent for cancer, and this therapeutic agent was subcutaneously administered to the tumor-bearing mice a total of 3 times at intervals of 1 week. As a result, on Day 31 after the administration of the therapeutic agent for cancer, complete regression of the tumor was achieved. On the other hand, in the negative control group to which PBS(-) was administered and the group to which poly I:C alone (50 µg) was administered, the mean tumor volumes on Day 31 after the administration were 1657 mm³ and 932 mm³, respectively.

[0143]

Further, a therapeutic agent for cancer wherein 100 µg (0.5 ml) of the recombinant murine PDS5A protein and 50 µg poly I:C were mixed was prepared, and subcutaneously administered to A/J mice a total of 3 times at intervals of 1 week, followed by transplantation of 1×10^6 N2a cells to the mice and evaluation of the anti-tumor effect (prophylactic model). Ten individuals were included in each group, and, as controls for comparison, a negative control group to which PBS(-) was administered and a group to which poly I:C alone (50 µg) was administered were provided. As a result, in the group to which the therapeutic agent for cancer was administered, no development of a tumor was observed even on Day 40 after the administration of the therapeutic agent for cancer. On the other hand, in the negative control group to which PBS(-) was administered and the group to which

poly I:C alone (50 μ g) was administered, the mean tumor volumes on Day 40 after the administration were 1989 mm³ and 1843 mm³, respectively.

[0144]

5 The same experiment was carried out also for a colon cancer model. The colon cancer cell line CT26 was subcutaneously transplanted to Balb/c mice (7 weeks old, male, purchased from Japan SLC) in an amount of 1×10^6 cells. When the tumor volume reached an average of 50 to 100 mm³ (typically 7 days after the inoculation of the tumor), the mice were randomly divided into groups each of which contains 10 individuals, and subjected to evaluation of the anti-tumor effect of the recombinant murine PDS5A protein (therapeutic model). With 100 μ g (0.5 ml) of the recombinant murine PDS5A protein purified as described above, 50 μ g of poly I:C was mixed to prepare a therapeutic agent for cancer, and this therapeutic agent was subcutaneously administered to the tumor-bearing mice a total of 3 times at intervals of 1 week. As a result, on Day 24 after the administration of the therapeutic agent for cancer, complete regression of the tumor was achieved. On the other hand, in the negative control group to which PBS(-) was administered and the group to which poly I:C alone (50 μ g) was administered, the mean tumor volumes on Day 24 after the administration were 1449 mm³ and 835 mm³, respectively.

[0145]

20 Further, a therapeutic agent for cancer wherein 100 μ g (0.5 ml) of the recombinant murine PDS5A protein and 50 μ g poly I:C were mixed was prepared, and subcutaneously administered to Balb/c mice a total of 3 times at intervals of 1 week, followed by transplantation of 1×10^6 CT26 cells to the mice and evaluation of the anti-tumor effect (prophylactic model). Ten individuals were included in each group, and, as controls for comparison, a negative control group to which PBS(-) was administered and a group to which poly I:C alone (50 μ g) was administered were provided. As a result, in the group to which the therapeutic agent for cancer

was administered, no development of a tumor was observed even on Day 31 after the administration of the therapeutic agent for cancer. On the other hand, in the negative control group to which PBS(-) was administered and the group to which poly I:C alone (50 μ g) was administered, the mean tumor volumes on Day 31 after the administration were 1781 mm³ and 1675 mm³, respectively.

[0146]

From these results, it was revealed that the recombinant PDS5A protein is effective for therapy and prophylaxis of cancer.

[0147]

10 (4) Anti-tumor Effect of Recombinant PDS5A Protein in Tumor-bearing Dog

The anti-tumor effect of the recombinant protein described in Example 5 below in 3 individuals of tumor-bearing patient dogs (3 individuals having a mammary gland tumor) having a tumor mass in the epidermis was evaluated. Before administration, the antibody titer against the recombinant protein in the serum of each patient dog was measured by the method described in Example 5 (3), and, as a result, an antibody titer higher than that of a healthy dog was detected. From these results, it was suggested that the protein having the amino acid sequence shown in SEQ ID NO:2 was expressed as a cancer antigen in the tumor tissue in the living body of these tumor-bearing patient dogs.

20 [0148]

With 500 μ g (2.5 ml) each of the recombinant PDS5A proteins (dog-derived and human-derived) purified as described above, the same amount of Freund's incomplete adjuvant (manufactured by Wako Pure Chemical Industries, Ltd.) was mixed to prepare 2 kinds of therapeutic agents for cancer, each of which was administered to a regional lymph node in the vicinity of the tumor a total of 3 times at 1-week intervals. As a result, complete regression of the tumor, which had had a size of about 500 mm³ or 1000 mm³ at the time of administration of each therapeutic

agent for cancer, was achieved on Day 13 or Day 21, respectively. On the other hand, in the negative control group to which PBS(-) was administered, the tumor volume, which had been about 800 mm³ at the time of administration of PBS, became 1625 mm³ on Day 21 after the administration.

5 [0149]

With 500 µg (2.5 ml) of the canine recombinant PDS5A protein purified as described in Example 5 below, the same amount of Freund's incomplete adjuvant (manufactured by Wako Pure Chemical Industries, Ltd.) was mixed to prepare a therapeutic agent for cancer, and this therapeutic agent was subcutaneously administered in the vicinity of the tumor in 1 individual each of patient dogs suffering from perianal adenocarcinoma and epidermal squamous cell carcinoma a total of 4 times at 1-week interval. As a result, complete regression of the tumor, which had had a size of about 370 mm³ or 280 mm³, respectively, at the time of administration of the therapeutic agent for cancer, was achieved on Day 35 or Day 42, respectively.

15 [0150]

(5) Detection of Cancer Using Recombinant PDS5A Protein

Blood was collected from 112 patient dogs wherein malignant tumor was found and 30 healthy dogs, and sera were separated therefrom. Using the canine PDS5A protein (SEQ ID NO:2) prepared in the above-described (2), the titer of antibodies specifically reactive with the protein in each serum was measured by the ELISA method. Immobilization of the prepared protein was carried out by placing 100 µL/well of the recombinant protein solution diluted to 5 µg/mL with phosphate-buffered saline in a 96-well Immobilizer Amino plate (manufactured by Nunc), followed by leaving the plate to stand at 4°C overnight. Blocking was carried out by adding 100 µL of 50 mM sodium bicarbonate buffer (pH 8.4) supplemented with 3% BSA (bovine serum albumin, manufactured by Sigma-Aldrich Co.) (hereinafter

referred to as the blocking solution) to each well and shaking the plate at room temperature for 1 hour. The sera were 1000-fold diluted with the blocking solution and added to the wells in an amount of 100 μ L/well, and the plate was shaken at room temperature for 3 hours to allow the reaction to proceed. The wells were washed 3 times with phosphate-buffered saline supplemented with 0.05% Tween 20 (manufactured by Wako Pure Chemical Industries, Ltd.) (hereinafter referred to as PBS-T), and 100 μ L/well of an HRP-modified anti-dog IgG antibody (Goat anti Dog IgG-h+I HRP conjugated: manufactured by BETHYL Laboratories) 3000-fold diluted with the blocking solution was added thereto, followed by shaking the plate at room temperature for 1 hour to allow the reaction to proceed. After washing the wells 3 times with PBS-T, 100 μ L/well of an HRP substrate TMB (1-Step Turbo TMB (tetramethylbenzidine), PIERCE) was added, and the enzyme-substrate reaction was allowed to proceed at room temperature for 30 minutes. Thereafter, 100 μ L/well of 0.5 M sulfuric acid solution (manufactured by Sigma-Aldrich Japan) was added to the wells to stop the reaction, and the absorbance at 450 nm was measured using a microplate reader. To prepare controls for comparison, experiments were carried out in the same manner as described above except that the prepared recombinant protein was not immobilized or except that the tumor-bearing dog serum was not reacted.

[0151]

All the 112 samples used for the above-described cancer diagnosis were those which had been definitely diagnosed as malignant by pathological diagnosis using extirpated tumor tissues.

[0152]

Specifically, the samples were those diagnosed as cancers such as malignant melanoma, malignant mixed tumor, hepatocellular carcinoma, basal cell carcinoma, intraoral tumor, perianal adenocarcinoma, anal sac tumor, anal sac apocrine

carcinoma, Sertoli cell tumor, vulva cancer, sebaceous adenocarcinoma, sebaceous
 epithelioma, sebaceous adenoma, sweat gland carcinoma, intranasal adenocarcinoma,
 nasal adenocarcinoma, thyroid cancer, colon cancer, bronchial adenocarcinoma,
 adenocarcinoma, ductal carcinoma, mammary adenocarcinoma, combined mammary
 5 adenocarcinoma, mammary gland malignant mixed tumor, intraductal papillary
 adenocarcinoma, fibrosarcoma, hemangiopericytoma, osteosarcoma, chondrosarcoma,
 soft tissue sarcoma, histiocytic sarcoma, myxosarcoma, undifferentiated sarcoma,
 lung cancer, mastocytoma, cutaneous leiomyoma, intra-abdominal leiomyoma,
 leiomyoma, squamous cell carcinoma, chronic lymphocytic leukemia, lymphoma,
 10 gastrointestinal lymphoma, digestive organ lymphoma, small cell or medium cell
 lymphoma, adrenomedullary tumor, granulosa cell tumor and pheochromocytoma.
 [0153]

Sera from these cancer-bearing dogs showed significantly higher antibody
 titers against the recombinant protein than sera from the healthy dogs. It was
 15 revealed that, by diagnosing a sample showing a value not less than twice as high as
 the average value in healthy dogs as malignant, 94 samples, which corresponds to
 83.9% of the malignant cases, could be successfully diagnosed as malignant. The
 types of the cancers in these 94 samples were as described below. It should be
 noted that, although a part of the samples were suffering from a plurality of types of
 20 cancers, each value shown below is the cumulative total for each type of cancer.
 [0154]

Malignant melanoma, 5 cases; lymphoma, 10 cases; granulosa cell tumor, 1
 case; hepatocellular carcinoma, 3 cases; malignant testicular tumor, 3 cases; intraoral
 tumor, 3 cases; perianal adenocarcinoma, 5 cases; sarcoma, 9 cases; mammary
 25 adenocarcinoma, 35 cases; lung cancer, 1 case; ductal carcinoma, 4 cases; sebaceous
 adenocarcinoma, 2 cases; mastocytoma, 5 cases; leiomyosarcoma, 1 case; squamous
 cell carcinoma, 4 cases; malignant mixed tumor, 2 cases; and hemangiopericytoma, 1

case.

[0155]

When cancer diagnosis was carried out in the same manner as described above using the human PDS5A protein (SEQ ID NO:44) prepared in the above-described (2), a similar result was obtained.

[0156]

From the above results, it was revealed that, by using the PDS5A protein to measure the titer of antibodies specifically reactive with the protein in the serum, detection and diagnosis of cancer is possible.

10 INDUSTRIAL APPLICABILITY

[0157]

The immunity-inducing agent of the present invention comprising a polypeptide that exerts an anti-tumor activity against various types of cancers is useful for therapy and/or prophylaxis of cancer, and/or detection of cancer.

SEQUENCE LISTING IN ELECTRONIC FORM

In accordance with Section 111(1) of the Patent Rules, this description contains a sequence listing in electronic form in ASCII text format (file: 76199-344 Seq 16-02-12 v1.txt).

A copy of the sequence listing in electronic form is available from the Canadian Intellectual Property Office.

The sequences in the sequence listing in electronic form are reproduced in the following table.

SEQUENCE TABLE

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 Gln Tyr Leu Pro Leu Ala Leu His Leu Ala Ser Glu Phe Phe Leu Arg
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 Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser His Asp Lys
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 Asp Thr Lys Ser Pro Gln Phe Asn Arg Tyr Phe Tyr Leu Leu Glu Asn
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Ala Pro Tyr Thr Ser His Asp Lys Leu Lys Asp Ile Phe Leu Phe Ile
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Arg Tyr Phe Tyr Leu Leu Glu Asn Leu Ala Trp Val Lys Ser Tyr Asn
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Ile Cys Phe Glu Leu Glu Asp Cys Asn Glu Ile Phe Ile Gln Leu Phe
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Arg Thr Leu Phe Ser Val Ile Asn Asn Ser His Asn Lys Lys Val Gln
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Met His Met Leu Asp Leu Met Ser Ser Ile Ile Met Glu Gly Asp Gly
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Val Thr Gln Glu Leu Leu Asp Ser Ile Leu Ile Asn Leu Ile Pro Ala
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His Lys Asn Leu Asn Lys Gln Ser Phe Asp Leu Ala Lys Val Leu Leu
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Lys Phe Ala Ser His Cys Leu Met Asn His Pro Asp Leu Ala Lys Asp
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Leu Cys Ala Lys Asp Pro Val Lys Glu Arg Arg Ala His Ala Arg Gln	
955 960 965	
tgt ttg tta aag aac atc agc atc cgc agg gag tac atc aaa cag aac	3102
Cys Leu Leu Lys Asn Ile Ser Ile Arg Arg Glu Tyr Ile Lys Gln Asn	
970 975 980 985	
ccc atg gcc act gag aaa tta ttg tca ctg ctg cct gaa tat gtg gtt	3150
Pro Met Ala Thr Glu Lys Leu Leu Ser Leu Leu Pro Glu Tyr Val Val	
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Pro Tyr Met Ile	His Leu Leu Ala His	Asp Pro Asp Phe Thr Arg	
1005	1010	1015	
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Ser Gln Asp Val	Asp Gln Leu Arg Asp	Ile Lys Glu Cys Leu Trp	
1020	1025	1030	
ttt atg ctt gaa	gtc tta atg aca aag	aat gaa aac aac agc cat	3285
Phe Met Leu Glu	Val Leu Met Thr Lys	Asn Glu Asn Asn Ser His	
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gca ttc atg aaa	aag atg gca gag aat	atc aag cta acc aga gac	3330
Ala Phe Met Lys	Lys Met Ala Glu Asn	Ile Lys Leu Thr Arg Asp	
1050	1055	1060	
gcc cag tct ccc	gat gaa tcc aag aca	aat gaa aaa ctt tat acg	3375
Ala Gln Ser Pro	Asp Glu Ser Lys Thr	Asn Glu Lys Leu Tyr Thr	
1065	1070	1075	
gtt tgt gac gtg	gct ctg tgt gtt ata	aat agt aaa agt gct ttg	3420
Val Cys Asp Val	Ala Leu Cys Val Ile	Asn Ser Lys Ser Ala Leu	
1080	1085	1090	
tgc aat gca gac	tca cca aag gac cca	gtc ctc cca atg aag ttc	3465
Cys Asn Ala Asp	Ser Pro Lys Asp Pro	Val Leu Pro Met Lys Phe	
1095	1100	1105	
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Phe Thr Gln Pro	Glu Lys Asp Phe Cys	Asn Asp Lys Ser Tyr Ile	
1110	1115	1120	
tca gaa gag aca	aga gtt ctt ctg tta	aca gga aag cca aag cct	3555
Ser Glu Glu Thr	Arg Val Leu Leu Leu	Thr Gly Lys Pro Lys Pro	
1125	1130	1135	
act gga gta tta	ggt aca gtg aac aag	cct tta tca gca acg gga	3600
Thr Gly Val Leu	Gly Thr Val Asn Lys	Pro Leu Ser Ala Thr Gly	
1140	1145	1150	
agg aag cct tat	gtt aga agc gcc ggc	aca gag act gga agc aat	3645
Arg Lys Pro Tyr	Val Arg Ser Ala Gly	Thr Glu Thr Gly Ser Asn	
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att aac gcc aat	tca gag ctg agt cct	tca gcc gga agt cgt tca	3690
Ile Asn Ala Asn	Ser Glu Leu Ser Pro	Ser Ala Gly Ser Arg Ser	
1170	1175	1180	
agg gaa cag agt	tca gag gca tca gaa	act gga gtt agt gaa aat	3735
Arg Glu Gln Ser	Ser Glu Ala Ser Glu	Thr Gly Val Ser Glu Asn	
1185	1190	1195	
gag gag aat cct	gtg aga ata att tct	gtc aca cct gta aag aat	3780
Glu Glu Asn Pro	Val Arg Ile Ile Ser	Val Thr Pro Val Lys Asn	
1200	1205	1210	

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 Ile Asp Thr Val Lys Asn Lys Glu Ile Asn Ser Asp Gln Ser Thr
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 Gln Gly Asn Ile Ser Ser Asp Arg Gly Lys Lys Arg Ile Val Thr
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 gca gct ggt gca gag aat atc caa aag cca gac gag aaa gta gat 3915
 Ala Ala Gly Ala Glu Asn Ile Gln Lys Pro Asp Glu Lys Val Asp
 1245 1250 1255

 gag tca gga ccg cct gcc cct tcc aaa ccc cgg aga gga cgt cgc 3960
 Glu Ser Gly Pro Pro Ala Pro Ser Lys Pro Arg Arg Gly Arg Arg
 1260 1265 1270

 ccc aaa tct gaa tct cag ggc aat gca acc aaa aac gat gat cta 4005
 Pro Lys Ser Glu Ser Gln Gly Asn Ala Thr Lys Asn Asp Asp Leu
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 aat aaa cct gtt agc aag gga agg aaa aga gct gca ggc agc cag 4050
 Asn Lys Pro Val Ser Lys Gly Arg Lys Arg Ala Ala Gly Ser Gln
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 Glu Ser Leu Glu Ala Gly Asn Ala Lys Ala Pro Lys Leu Gln Asp
 1305 1310 1315

 gga gcc aaa aag gca gtt cca gca gag aga caa att gat tta caa 4140
 Gly Ala Lys Lys Ala Val Pro Ala Glu Arg Gln Ile Asp Leu Gln
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 agg taa tgtgacccca ctcaccccca ccttgctcagc agtgggaatg gctggcaata 4196
 Arg

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 Ser Ala Asp Gly Lys Ile Ala Tyr Pro Pro Gly Val Lys Glu Ile Thr
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 Asp Lys Ile Thr Thr Asp Glu Met Ile Lys Arg Leu Lys Met Val Val
 35 40 45
 Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Asp Glu Lys Gln Gln
 50 55 60

Tyr	Leu	Pro	Leu	Ala	Leu	His	Leu	Ala	Ser	Glu	Phe	Phe	Leu	Arg	Asn	65	70	75	80
Pro	Asn	Lys	Asp	Val	Arg	Leu	Leu	Val	Ala	Cys	Cys	Leu	Ala	Asp	Ile	85	90	95	
Phe	Arg	Ile	Tyr	Ala	Pro	Glu	Ala	Pro	Tyr	Thr	Ser	His	Asp	Lys	Leu	100	105	110	
Lys	Asp	Ile	Phe	Leu	Phe	Ile	Thr	Arg	Gln	Leu	Lys	Gly	Leu	Glu	Asp	115	120	125	
Thr	Lys	Ser	Pro	Gln	Phe	Asn	Arg	Tyr	Phe	Tyr	Leu	Leu	Glu	Asn	Leu	130	135	140	
Ala	Trp	Val	Lys	Ser	Tyr	Asn	Ile	Cys	Phe	Glu	Leu	Glu	Asp	Cys	Asn	145	150	155	160
Glu	Ile	Phe	Ile	Gln	Leu	Phe	Arg	Thr	Leu	Phe	Ser	Val	Ile	Asn	Asn	165	170	175	
Ser	His	Asn	Thr	Lys	Val	Gln	Met	His	Met	Leu	Asp	Leu	Met	Ser	Ser	180	185	190	
Ile	Ile	Met	Glu	Gly	Asp	Gly	Val	Thr	Gln	Glu	Leu	Leu	Asp	Ser	Ile	195	200	205	
Leu	Ile	Asn	Leu	Ile	Pro	Ala	His	Lys	Asn	Leu	Asn	Lys	Gln	Ser	Phe	210	215	220	
Asp	Leu	Ala	Lys	Val	Leu	Leu	Lys	Arg	Thr	Val	Gln	Thr	Ile	Glu	Ala	225	230	235	240
Cys	Ile	Ala	Asn	Phe	Phe	Asn	Gln	Val	Leu	Val	Leu	Gly	Arg	Ser	Ser	245	250	255	
Val	Ser	Asp	Leu	Ser	Glu	His	Val	Phe	Asp	Leu	Ile	Gln	Glu	Leu	Phe	260	265	270	
Ala	Ile	Asp	Pro	Gln	Leu	Leu	Leu	Ser	Val	Met	Pro	Gln	Leu	Glu	Phe	275	280	285	
Lys	Leu	Lys	Ser	Asn	Asp	Gly	Glu	Glu	Arg	Leu	Ala	Val	Val	Arg	Leu	290	295	300	
Leu	Ala	Lys	Leu	Phe	Gly	Ser	Lys	Asp	Ser	Asp	Leu	Ala	Thr	Gln	Asn	305	310	315	320
Arg	Pro	Leu	Trp	Gln	Cys	Phe	Leu	Gly	Arg	Phe	Asn	Asp	Ile	His	Val	325	330	335	
Pro	Val	Arg	Leu	Glu	Ser	Val	Lys	Phe	Ala	Ser	His	Cys	Leu	Met	Asn	340	345	350	
His	Pro	Asp	Leu	Ala	Lys	Asp	Leu	Thr	Glu	Tyr	Leu	Lys	Val	Arg	Ser	355	360	365	
His	Asp	Pro	Glu	Glu	Ala	Ile	Arg	His	Asp	Val	Ile	Val	Thr	Ile	Ile	370	375	380	
Thr	Ala	Ala	Lys	Arg	Asp	Leu	Ala	Leu	Val	Asn	Asp	Gln	Leu	Leu	Gly	385	390	395	400
Phe	Val	Arg	Glu	Arg	Thr	Leu	Asp	Lys	Arg	Trp	Arg	Val	Arg	Lys	Glu	405	410	415	
Ala	Met	Met	Gly	Leu	Ala	Gln	Leu	Tyr	Lys	Lys	Tyr	Cys	Leu	His	Gly	420	425	430	
Glu	Ala	Gly	Lys	Glu	Ala	Ala	Glu	Lys	Val	Ser	Trp	Ile	Lys	Asp	Lys	435	440	445	
Leu	Leu	His	Ile	Tyr	Tyr	Gln	Asn	Ser	Ile	Asp	Asp	Lys	Leu	Leu	Val	450	455	460	
Glu	Lys	Ile	Phe	Ala	Gln	Tyr	Leu	Val	Pro	His	Asn	Leu	Glu	Thr	Glu	465	470	475	480
Glu	Arg	Met	Lys	Cys	Leu	Tyr	Tyr	Leu	Tyr	Ala	Ser	Leu	Asp	Pro	Asn	485	490	495	
Ala	Val	Lys	Ala	Leu	Asn	Glu	Met	Trp	Lys	Cys	Gln	Asn	Met	Leu	Arg	500	505	510	

Ser	His	Val	Arg	Glu	Leu	Leu	Asp	Leu	His	Lys	Gln	Pro	Thr	Ser	Glu
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Ala	Asn	Cys	Ser	Ala	Met	Phe	Gly	Lys	Leu	Met	Thr	Ile	Ala	Lys	Asn
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Leu	Pro	Asp	Pro	Gly	Lys	Ala	Gln	Asp	Phe	Val	Lys	Lys	Phe	Asn	Gln
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Val	Leu	Gly	Asp	Asp	Glu	Lys	Leu	Arg	Ser	Gln	Leu	Glu	Leu	Leu	Ile
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Ser	Pro	Thr	Cys	Ser	Cys	Lys	Gln	Ala	Asp	Val	Cys	Val	Arg	Glu	Ile
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Ala	Arg	Lys	Leu	Ala	Asn	Pro	Lys	Gln	Pro	Thr	Asn	Pro	Phe	Leu	Glu
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Met	Val	Lys	Phe	Leu	Leu	Glu	Arg	Ile	Ala	Pro	Val	His	Ile	Asp	Ser
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Glu	Ala	Ile	Ser	Ala	Leu	Val	Lys	Leu	Met	Asn	Lys	Ser	Ile	Glu	Gly
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Thr	Ala	Asp	Asp	Glu	Glu	Glu	Gly	Val	Ser	Pro	Asp	Ser	Ala	Ile	Arg
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Ser	Gly	Leu	Glu	Leu	Leu	Lys	Val	Leu	Ser	Phe	Thr	His	Pro	Thr	Ser
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Phe	His	Ser	Ala	Glu	Thr	Tyr	Glu	Ser	Leu	Leu	Gln	Cys	Leu	Arg	Met
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Glu	Asp	Asp	Lys	Val	Ala	Glu	Ala	Ala	Ile	Gln	Ile	Phe	Arg	Asn	Thr
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Gly	His	Lys	Ile	Glu	Thr	Asp	Leu	Pro	Gln	Ile	Arg	Ser	Thr	Leu	Ile
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Pro	Ile	Leu	His	Gln	Lys	Ala	Lys	Arg	Gly	Thr	Pro	His	Gln	Ala	Lys
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Gln	Ala	Val	His	Cys	Ile	His	Ala	Ile	Phe	Ser	Asn	Lys	Glu	Val	Gln
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Leu	Ala	Gln	Ile	Phe	Glu	Pro	Leu	Ser	Arg	Ser	Leu	Asn	Ala	Asp	Val
		755					760					765			
Pro	Glu	Gln	Leu	Ile	Thr	Pro	Leu	Val	Ser	Leu	Gly	His	Ile	Ser	Met
	770					775					780				
Leu	Ala	Pro	Asp	Gln	Phe	Ala	Ser	Pro	Met	Lys	Ser	Val	Val	Ala	Asn
785					790					795					800
Phe	Ile	Val	Lys	Asp	Leu	Leu	Met	Asn	Asp	Arg	Ser	Thr	Gly	Glu	Lys
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Asn	Gly	Lys	Leu	Trp	Ser	Pro	Asp	Glu	Glu	Val	Ser	Pro	Glu	Val	Leu
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Ala	Lys	Val	Gln	Ala	Ile	Lys	Leu	Leu	Val	Arg	Trp	Leu	Leu	Gly	Met
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Lys	Asn	Asn	Gln	Ser	Lys	Ser	Ala	Asn	Ser	Thr	Leu	Arg	Leu	Leu	Ser
	850					855					860				
Ala	Met	Leu	Val	Ser	Glu	Gly	Asp	Leu	Thr	Glu	Gln	Lys	Arg	Ile	Ser
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Lys	Ser	Asp	Met	Ser	Arg	Leu	Arg	Leu	Ala	Ala	Gly	Ser	Ala	Ile	Met
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Lys	Leu	Ala	Gln	Glu	Pro	Cys	Tyr	His	Glu	Ile	Ile	Thr	Pro	Glu	Gln
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Phe	Gln	Leu	Cys	Ala	Leu	Val	Ile	Asn	Asp	Glu	Cys	Tyr	Gln	Val	Arg
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Gln	Ile	Phe	Ala	Gln	Lys	Leu	His	Lys	Ala	Leu	Val	Lys	Leu	Leu	Leu
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 Lys Thr Asn Glu Lys Leu Tyr Thr Val Cys Asp Val Ala Leu Cys
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 Asp Pro Val Leu Pro Met Lys Phe Phe Thr Gln Pro Glu Lys Asp
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Val Ser Ala Asp Gly Lys Ile Ala Tyr Pro Pro Gly Val Lys Glu Ile	
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acc gac aag atc acc acg gac gaa atg atc aaa cga ctg aag atg gta	144
Thr Asp Lys Ile Thr Thr Asp Glu Met Ile Lys Arg Leu Lys Met Val	
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Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Asp Glu Lys Gln	
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Gln Tyr Leu Pro Leu Ala Leu His Leu Ala Ser Glu Phe Phe Leu Arg	
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Asn Pro Asn Lys Asp Val Arg Leu Leu Val Ala Cys Cys Leu Ala Asp	
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Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser His Asp Lys	
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115 120 125	
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Asp Thr Lys Ser Pro Gln Phe Asn Arg Tyr Phe Tyr Leu Leu Glu Asn	
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Arg Met Lys Cys Leu Tyr Tyr Leu Tyr Ala Ser Leu Asp Pro Asn Ala	
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Val Lys Ala Leu Asn Glu Met Trp Lys Cys Gln Asn Met Leu Arg Ser	
465 470 475 480	
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485 490 495	
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Asn Cys Ser Ala Met Phe Gly Lys Leu Met Thr Ile Ala Lys Asn Leu	
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Leu Gly Asp Asp Glu Lys Leu Arg Ser Gln Leu Glu Leu Leu Ile Ser	
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Ala Asp Asp Glu Glu Glu Gly Val Ser Pro Asp Thr Ala Ile Arg Ser	
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gga ctt gaa ctt ctt aag gtt ctg tct ttc aca cat cct acc tcg ttc	1920
Gly Leu Glu Leu Leu Lys Val Leu Ser Phe Thr His Pro Thr Ser Phe	
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cac tct gca gag aca tat gag tcc ctg ttg cag tgc ctc aga atg gaa	1968
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Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Asp Glu Lys Gln	
50 55 60	
cag tat ctc cca ctc gcc ttg cat ctt gca tct gaa ttt ttc ctc agg	240
Gln Tyr Leu Pro Leu Ala Leu His Leu Ala Ser Glu Phe Phe Leu Arg	
65 70 75 80	
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Asn Pro Asn Lys Asp Val Arg Leu Leu Val Ala Cys Cys Leu Ala Asp	
85 90 95	
atc ttt cga atc tat gcc cca gaa gct cca tat act tcc cat gat aaa	336
Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser His Asp Lys	
100 105 110	
ctt aag gac ata ttt ttg ttt att acc aga caa tta aaa ggt ttg gag	384
Leu Lys Asp Ile Phe Leu Phe Ile Thr Arg Gln Leu Lys Gly Leu Glu	
115 120 125	
gat aca aag agt ccg cag ttt aat aga tac ttt tat tta tta gag aat	432
Asp Thr Lys Ser Pro Gln Phe Asn Arg Tyr Phe Tyr Leu Leu Glu Asn	
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Leu Ala Trp Val Lys Ser Tyr Asn Ile Cys Phe Glu Leu Glu Asp Cys	
145 150 155 160	
aat gaa att ttt att cag ctt ttt agg act ctc ttc tca gtg atc aac	528
Asn Glu Ile Phe Ile Gln Leu Phe Arg Thr Leu Phe Ser Val Ile Asn	
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aat agc cac aat aag aag gta caa atg cac atg cta gac ttg atg agt	576
Asn Ser His Asn Lys Lys Val Gln Met His Met Leu Asp Leu Met Ser	
180 185 190	
tct atc atc atg gaa ggt gat gga gtt act caa gaa tta ttg gac tcc	624
Ser Ile Ile Met Glu Gly Asp Gly Val Thr Gln Glu Leu Leu Asp Ser	
195 200 205	

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aac cac cca gat tta gca aag gac ctc aca gaa tat ttg aaa gtt aga Asn His Pro Asp Leu Ala Lys Asp Leu Thr Glu Tyr Leu Lys Val Arg 355 360 365	1104
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ata aca gct gcc aaa aga gac ctt gcc tta gta aat gat cag ctg ctt Ile Thr Ala Ala Lys Arg Asp Leu Ala Leu Val Asn Asp Gln Leu Leu 385 390 395 400	1200
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tcg ttc cac tct gca gag acg tat gag tcc ctg tta cag tgc ctc aga	2064
Ser Phe His Ser Ala Glu Thr Tyr Glu Ser Leu Leu Gln Cys Leu Arg	
675 680 685	
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Met Glu Asp Asp Lys Val Ala Glu Ala Ala Ile Gln Ile Phe Arg Asn	
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Thr Gly His Lys Ile Glu Thr Asp Leu Pro Gln Ile Arg Ser Thr Leu	
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Ile Pro Ile Leu His Gln Lys Ala Lys Arg Gly Thr Pro His Gln Ala	
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Lys Gln Ala Val His Cys Ile His Ala Ile Phe Thr Asn Lys Glu Val	
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Gln Leu Ala Gln Ile Phe Glu Pro Leu Ser Arg Ser Leu Asn Ala Asp	
755 760 765	
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Val Pro Glu Gln Leu Ile Thr Pro Leu Val Ser Leu Gly His Ile Ser	
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805 810 815	
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Lys Asn Gly Lys Leu Trp Ser Pro Asp Glu Glu Val Ser Pro Glu Val	
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Leu Ala Lys Val Gln Ala Ile Lys Leu Leu Val Arg Trp Leu Leu Gly	
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885 890 895	
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915 920 925	
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945 950 955 960	
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Val Lys Glu Arg Arg Ala His Ala Arg Gln Cys Leu Leu Lys Asn Ile	
965 970 975	
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Ser Ile Arg Arg Glu Tyr Ile Lys Gln Asn Pro Met Ala Thr Glu Lys	
980 985 990	
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Leu Ala His Asp Pro Asp Phe Thr Arg Ser Gln Asp Val Asp Gln	
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Cys Val Ile Asn Ser Lys Ser Ala Leu Cys Asn Ala Asp Ser Pro	
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Ile Ile Ser Val Thr Pro Val	Lys Asn Ile Asp Pro Val Lys Asn	
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Lys Glu Ile Asn Ser Asp Gln	Ala Thr Gln Gly Asn Ile Ser Ser	
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Asp Arg Gly Lys Lys Arg Thr	Val Thr Ala Ala Gly Thr Glu Asn	
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Ile Gln Gln Lys Thr Asp Glu	Lys Val Asp Glu Ser Gly Pro Pro	
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Ala Pro Ser Lys Pro Arg Arg	Gly Arg Arg Pro Lys Ser Glu Ser	
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Gln Gly Asn Ala Thr Lys Asn	Asp Asp Ile Asn Lys Pro Leu Ser	
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 Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Asp Glu Lys Gln
 50 55 60
 Gln Tyr Leu Pro Leu Ala Leu His Leu Ala Ser Glu Phe Phe Leu Arg
 65 70 75 80
 Asn Pro Asn Lys Asp Val Arg Leu Leu Val Ala Cys Cys Leu Ala Asp
 85 90 95
 Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser His Asp Lys
 100 105 110
 Leu Lys Asp Ile Phe Leu Phe Ile Thr Arg Gln Leu Lys Gly Leu Glu
 115 120 125
 Asp Thr Lys Ser Pro Gln Phe Asn Arg Tyr Phe Tyr Leu Leu Glu Asn
 130 135 140
 Leu Ala Trp Val Lys Ser Tyr Asn Ile Cys Phe Glu Leu Glu Asp Cys
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 Asn Glu Ile Phe Ile Gln Leu Phe Arg Thr Leu Phe Ser Val Ile Asn
 165 170 175
 Asn Ser His Asn Lys Lys Val Gln Met His Met Leu Asp Leu Met Ser
 180 185 190
 Ser Ile Ile Met Glu Gly Asp Gly Val Thr Gln Glu Leu Leu Asp Ser
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 Ile Leu Ile Asn Leu Ile Pro Ala His Lys Asn Leu Asn Lys Gln Ser
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 Ala Cys Ile Ala Asn Phe Phe Asn Gln Val Leu Val Leu Gly Arg Ser
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 Ser Val Ser Asp Leu Ser Glu His Val Phe Asp Leu Ile Gln Glu Leu
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 Phe Lys Leu Lys Ser Asn Asp Gly Glu Glu Arg Leu Ala Val Val Arg
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 Asn His Pro Asp Leu Ala Lys Asp Leu Thr Glu Tyr Leu Lys Val Arg
 355 360 365
 Ser His Asp Pro Glu Glu Ala Ile Arg His Asp Val Ile Val Thr Ile
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 Ile Thr Ala Ala Lys Arg Asp Leu Ala Leu Val Asn Asp Gln Leu Leu
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Gly	Phe	Val	Arg	Glu	Arg	Thr	Leu	Asp	Lys	Arg	Trp	Arg	Val	Arg	Lys	405	410	415
Glu	Ala	Met	Met	Gly	Leu	Ala	Gln	Leu	Tyr	Lys	Lys	Tyr	Cys	Leu	His	420	425	430
Gly	Glu	Ala	Gly	Lys	Glu	Ala	Ala	Glu	Lys	Val	Ser	Trp	Ile	Lys	Asp	435	440	445
Lys	Leu	Leu	His	Ile	Tyr	Tyr	Gln	Asn	Ser	Ile	Asp	Asp	Lys	Leu	Leu	450	455	460
Val	Glu	Lys	Ile	Phe	Ala	Gln	Tyr	Leu	Val	Pro	His	Asn	Leu	Glu	Thr	465	470	475
Glu	Glu	Arg	Met	Lys	Cys	Leu	Tyr	Tyr	Leu	Tyr	Ala	Ser	Leu	Asp	Pro	485	490	495
Asn	Ala	Val	Lys	Ala	Leu	Asn	Glu	Met	Trp	Lys	Cys	Gln	Asn	Met	Leu	500	505	510
Arg	Ser	His	Val	Arg	Glu	Leu	Leu	Asp	Leu	His	Lys	Gln	Pro	Thr	Ser	515	520	525
Glu	Ala	Asn	Cys	Ser	Ala	Met	Phe	Gly	Lys	Leu	Met	Thr	Ile	Ala	Lys	530	535	540
Asn	Leu	Pro	Asp	Pro	Gly	Lys	Ala	Gln	Asp	Phe	Val	Lys	Lys	Phe	Asn	545	550	555
Gln	Val	Leu	Gly	Asp	Asp	Glu	Lys	Leu	Arg	Ser	Gln	Leu	Glu	Leu	Leu	565	570	575
Ile	Ser	Pro	Thr	Cys	Ser	Cys	Lys	Gln	Ala	Asp	Val	Cys	Val	Arg	Glu	580	585	590
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Lys	Asn	Gly	Lys	Leu	Trp	Ser	Pro	Asp	Glu	Glu	Val	Ser	Pro	Glu	Val	820	825	830
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Ser	His	Asp	Lys	Leu	Lys	Asp	Ile	Phe	Leu	Phe	Ile	Thr	Arg	Gln	Leu		
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Pro	His	Gln	Ala	Lys	Gln	Ala	Val	His	Cys	Ile	His	Ala	Ile	Phe	Ser
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Leu															

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 Gly Ser Ala Ile Met Lys Leu Ala Gln Glu Pro Cys Tyr His Glu Ile
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 Val Ser Ala Asp Gly Lys Ile Ala Tyr Pro Pro Gly Val Lys Glu Ile
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 Thr Asp Lys Ile Thr Thr Asp Glu Met Ile Lys Arg Leu Lys Met Val
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 Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Asp Glu Lys Gln
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 Gln Tyr Leu Pro Leu Ala Leu His Leu Ala Ser Glu Phe Phe Leu Arg
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Gln Leu Ala Gln Ile Phe Glu Pro Leu Ser Arg Ser Leu Asn Ala Asp	
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Ser Lys Ser Asp Met Ser Arg Leu Arg Leu Ala Ala Gly Ser Ala Ile	
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Ser Ile Arg Arg Glu Tyr Ile Lys Gln Asn Pro Met Ala Thr Glu Lys	
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          35          40          45
Val Lys Thr Phe Met Asp Met Asp Gln Asp Ser Glu Asp Glu Lys Gln
          50          55          60
Gln Tyr Leu Pro Leu Ala Leu His Leu Ala Ser Glu Phe Phe Leu Arg
65          70          75          80
Asn Pro Asn Lys Asp Val Arg Leu Leu Val Ala Cys Cys Leu Ala Asp
          85          90          95
Ile Phe Arg Ile Tyr Ala Pro Glu Ala Pro Tyr Thr Ser His Asp Lys
          100          105          110
Leu Lys Asp Ile Phe Leu Phe Ile Thr Arg Gln Leu Lys Gly Leu Glu
          115          120          125
Asp Thr Lys Ser Pro Gln Phe Asn Arg Tyr Phe Tyr Leu Leu Glu Asn
          130          135          140
Leu Ala Trp Val Lys Ser Tyr Asn Ile Cys Phe Glu Leu Glu Asp Cys
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Asn Glu Ile Phe Ile Gln Leu Phe Arg Thr Leu Phe Ser Val Ile Asn
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Asn Ser His Asn Lys Lys Val Gln Met His Met Leu Asp Leu Met Ser
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CLAIMS:

1. An immunity-inducing agent for prophylaxis or therapy of a PDS5A-expressing cancer in an animal, the agent comprising:
 - (a) at least one polypeptide, the amino acid sequence of which is shown in any one of
5 SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, said polypeptide(s) having an immunity-inducing activity/activities, or
 - (b) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) as defined in (a), and which express(es) said polypeptide(s) in vivo.
- 10 2. The immunity-inducing agent for prophylaxis or therapy according to claim 1, comprising at least one polypeptide as defined in (a).
3. An immunity-inducing agent for prophylaxis or therapy of a PDS5A-expressing cancer in an animal, the agent comprising:
 - (a) at least one polypeptide, the amino acid sequence of which is shown in any one of
SEQ ID NOs:27 to 35, said polypeptide(s) having an immunity-inducing activity/activities, or
 - 15 (b) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) defined in (a), and which express(es) said polypeptide(s) in vivo.
4. The immunity-inducing agent for prophylaxis or therapy according to claim 3, comprising at least one polypeptide as defined in (a).
5. The immunity-inducing agent for prophylaxis or therapy according to any one of
20 claims 1 to 4, wherein said PDS5A-expressing cancer is breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, perianal adenocarcinoma, neuroblastoma or leukemia.
6. The immunity-inducing agent for prophylaxis or therapy according to any one of claims 1 to 5, further comprising an immunoenhancer.

7. A polypeptide, the amino acid sequence of which is shown in any one of SEQ ID NOs:27, 28 and 30 to 35.
8. A method for detecting a PDS5A-expressing cancer, said method comprising measurement of anti PDS5A antibodies that bind specifically to a polypeptide, the amino acid
5 sequence of which is shown in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, in a sample separated from a living body.
9. Use of:
- (a) at least one polypeptide, the amino acid sequence of which is shown in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12 and 44, said polypeptide(s) having an immunity-inducing
10 activity/activities, or
- (b) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) as defined in (a), and which express(es) said polypeptide(s) in vivo;
for inducing immunity against a PDS5A-expressing cancer.
10. Use of:
- 15 (a) at least one polypeptide, the amino acid sequence of which is shown in any one of SEQ ID NOs:27 to 35, said polypeptide(s) having an immunity-inducing activity/activities, or
- (b) a recombinant vector(s) which comprise(s) a polynucleotide(s) encoding said polypeptide(s) as defined in (a), and which express(es) said polypeptide(s) in vivo;
for inducing immunity against a PDS5A-expressing cancer.
- 20 11. The use according to claim 9 or 10, wherein said PDS5A-expressing cancer is breast cancer, brain tumor, esophagus cancer, lung cancer, renal cancer, colon cancer, perianal adenocarcinoma, neuroblastoma or leukemia.
12. The use according to any one of claims 9 to 11, further comprising use of an immunoenhancer.

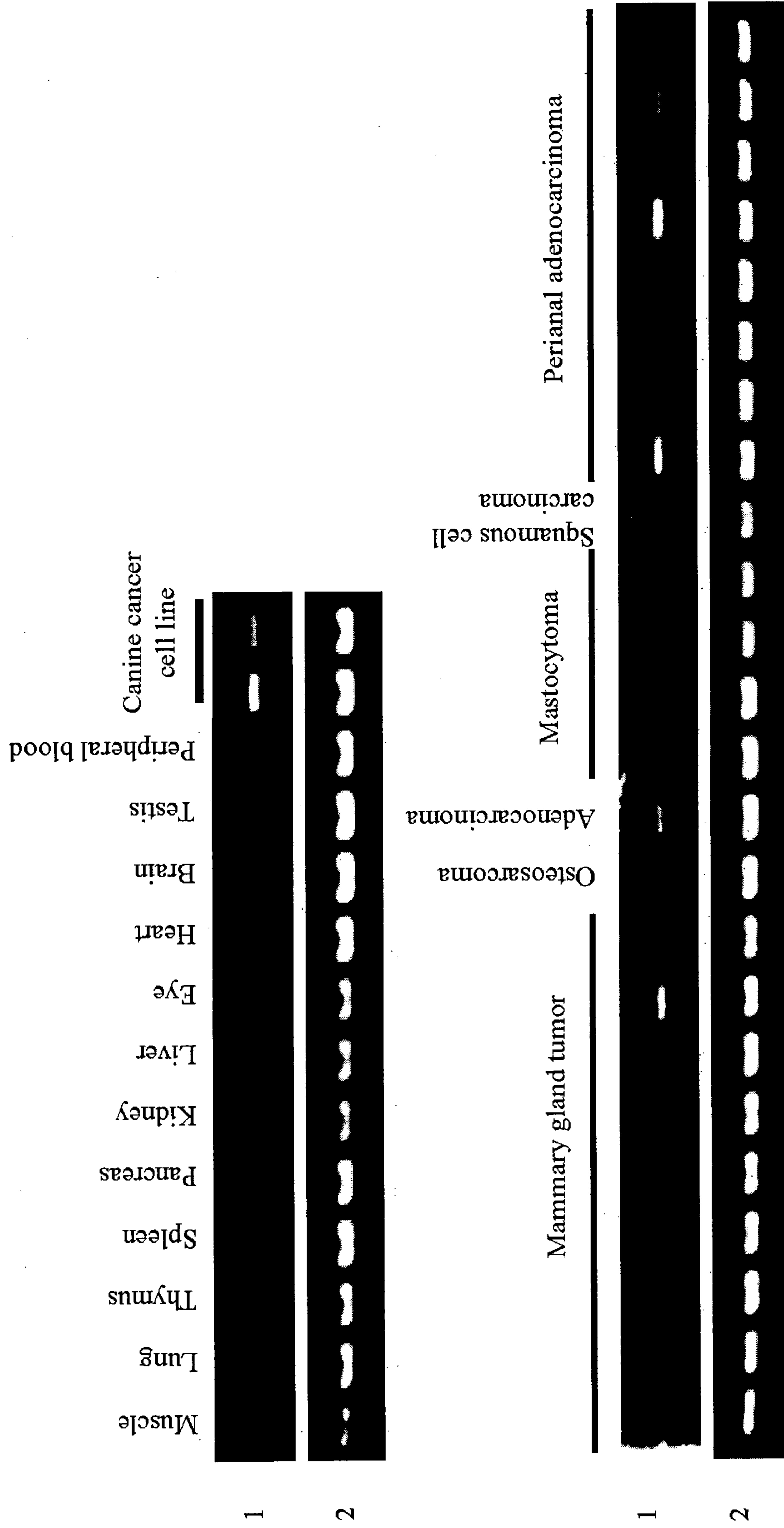


Fig.1

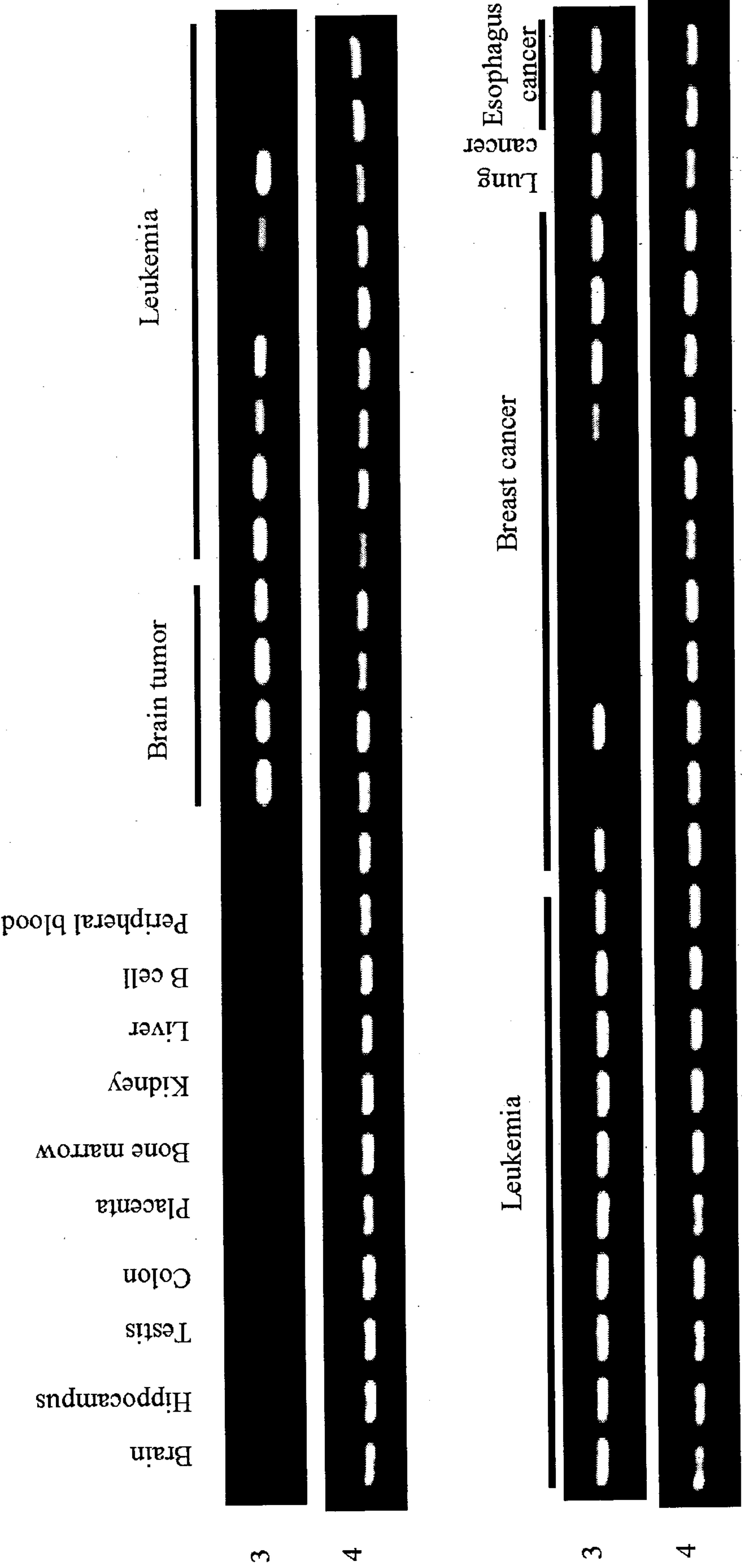


Fig.2

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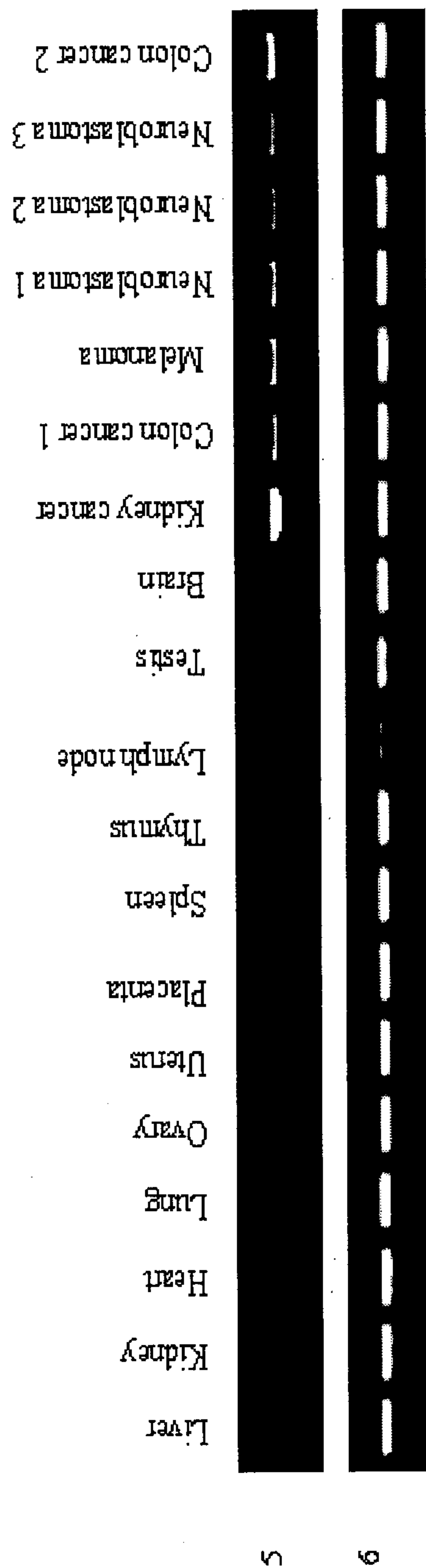


Fig.3

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Anti-tumor effect (therapeutic model - neuroblastoma cell line)

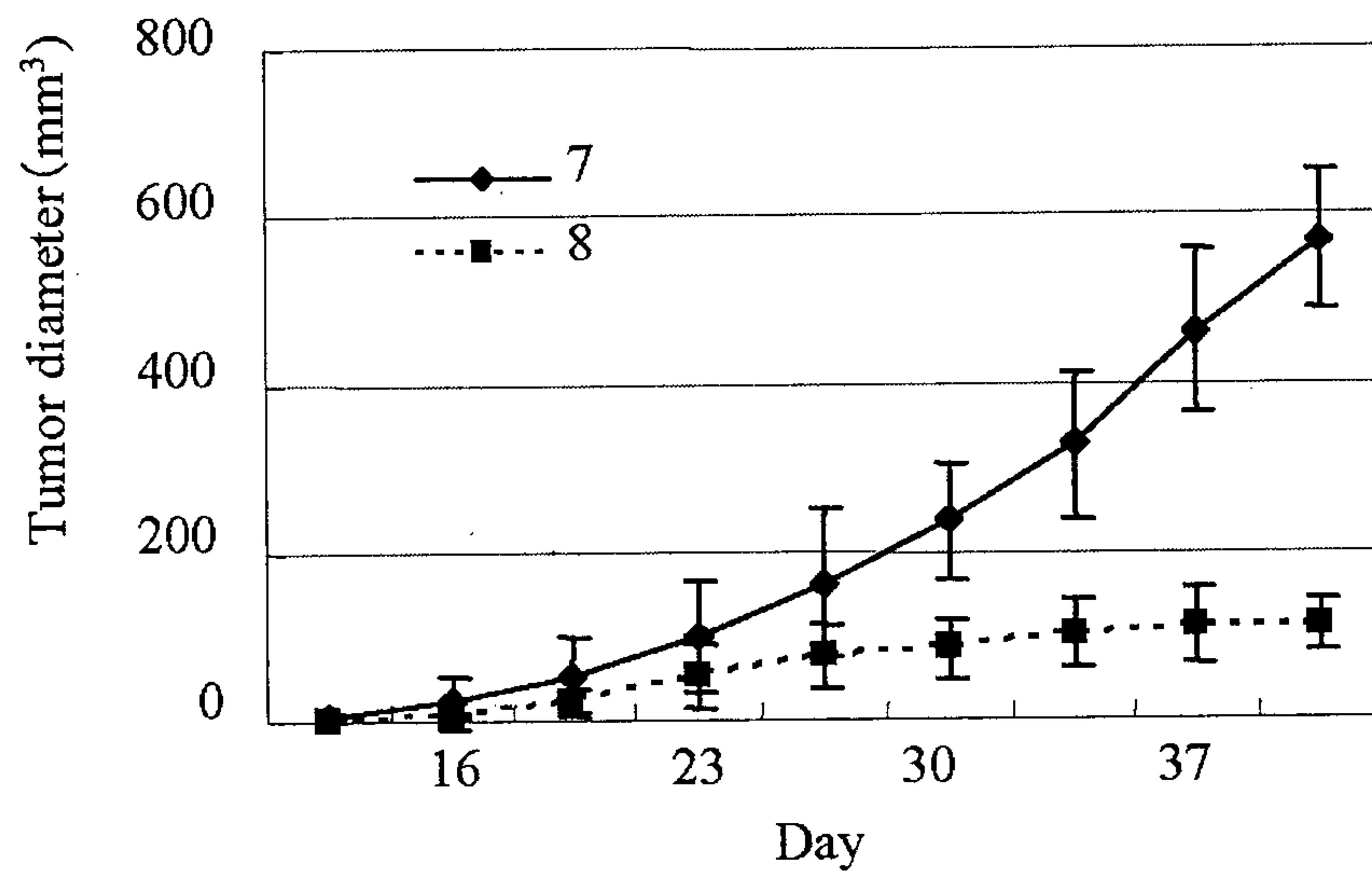


Fig.4

Anti-tumor effect (prophylactic model - neuroblastoma cell line)

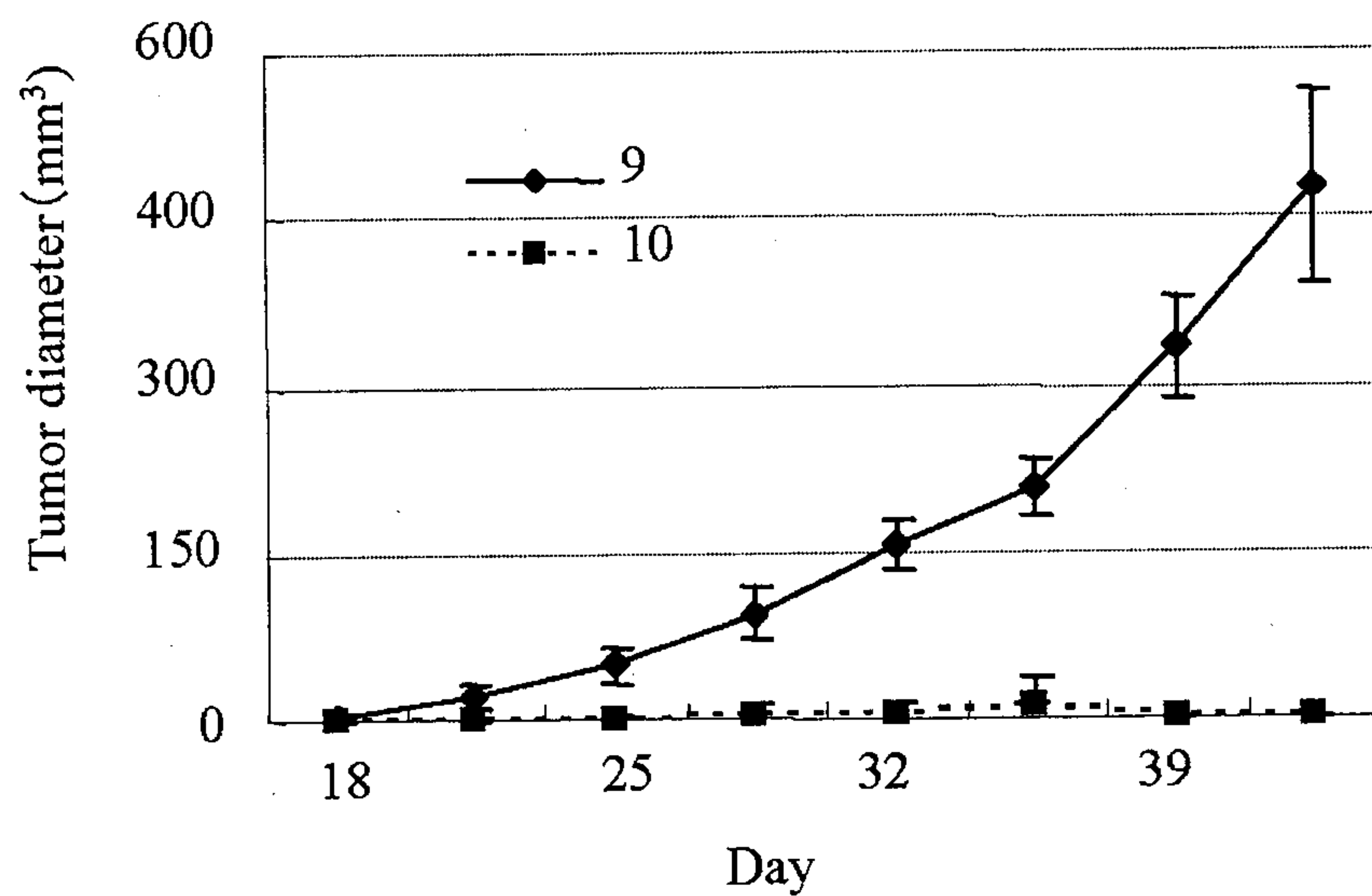


Fig.5

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Survival rate (therapeutic model - neuroblastoma cell line)

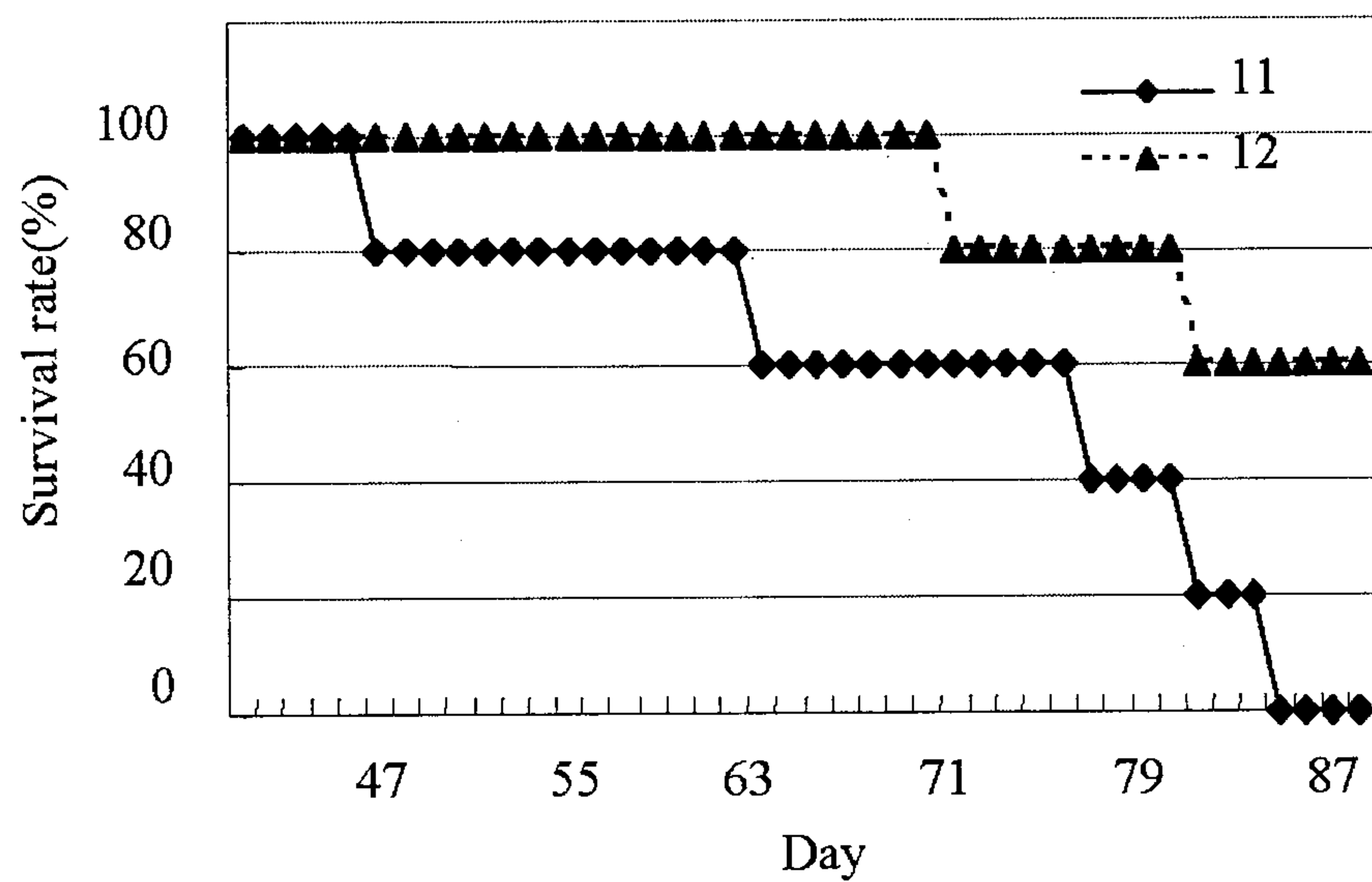


Fig.6

Survival rate (prophylactic model - neuroblastoma cell line)

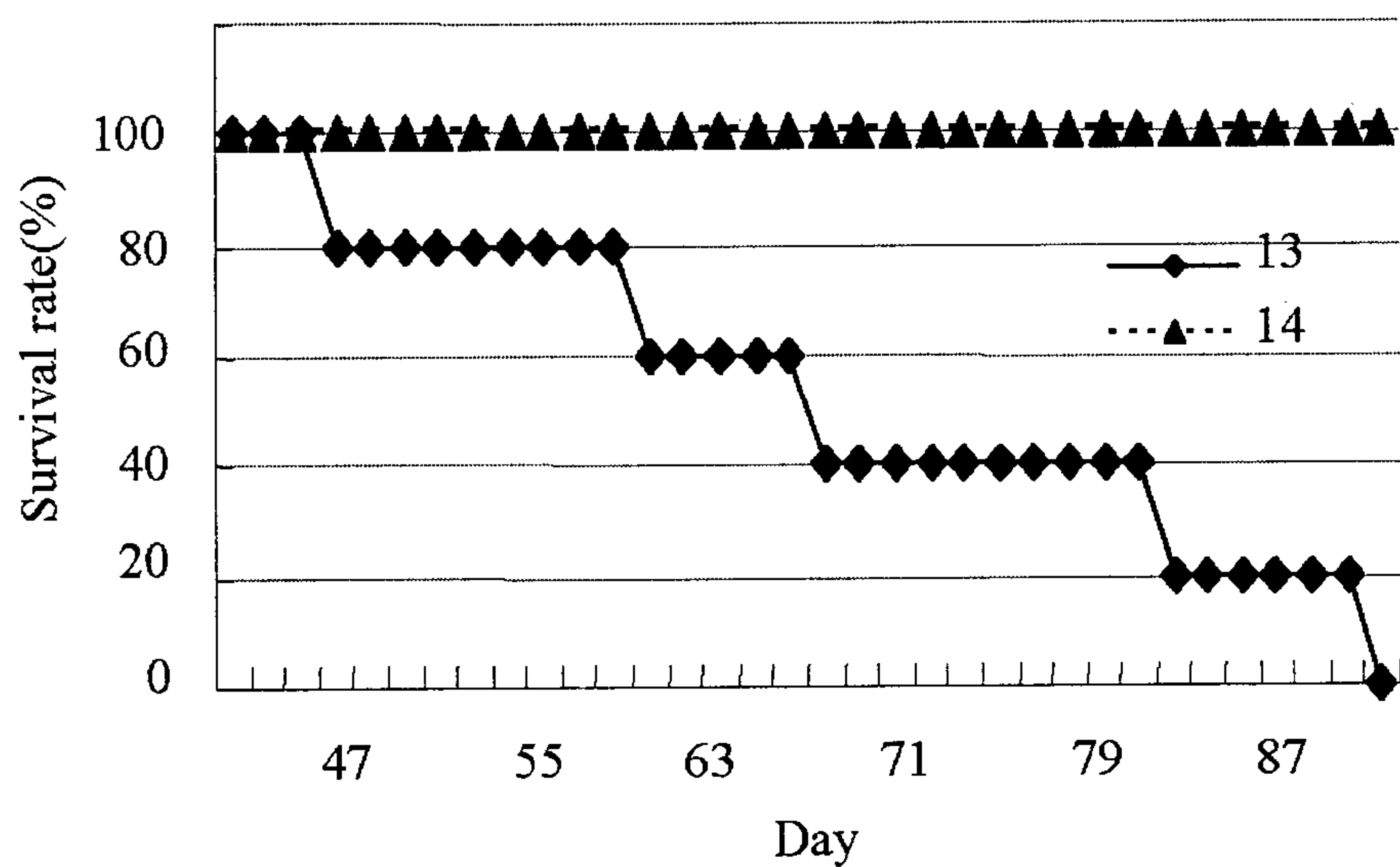


Fig.7

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Anti-tumor effect (therapeutic model - colon cancer cell line)

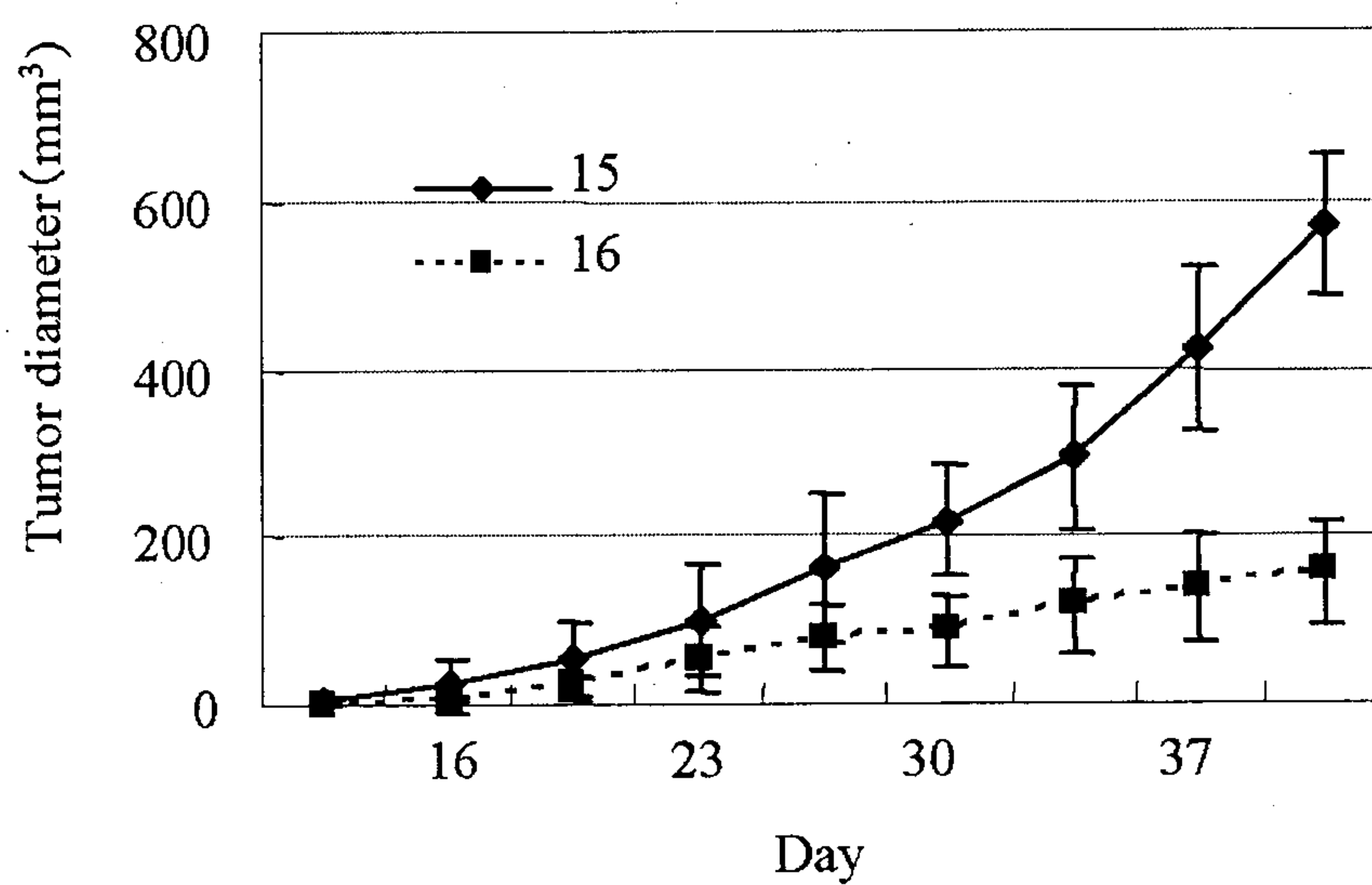


Fig.8

Anti-tumor effect (prophylactic model - colon cancer cell line)

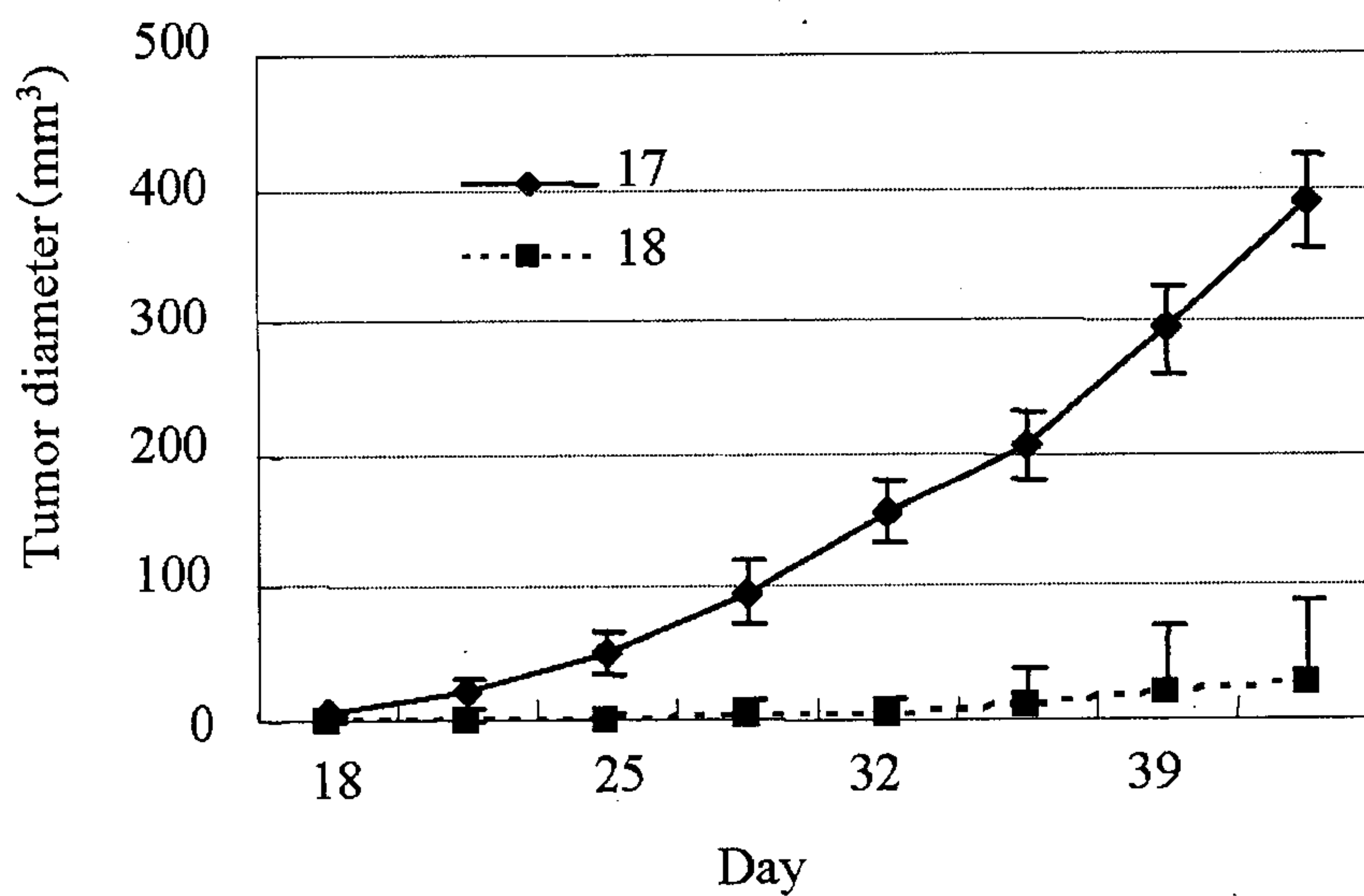


Fig.9

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Survival rate (therapeutic model - colon cancer cell line)

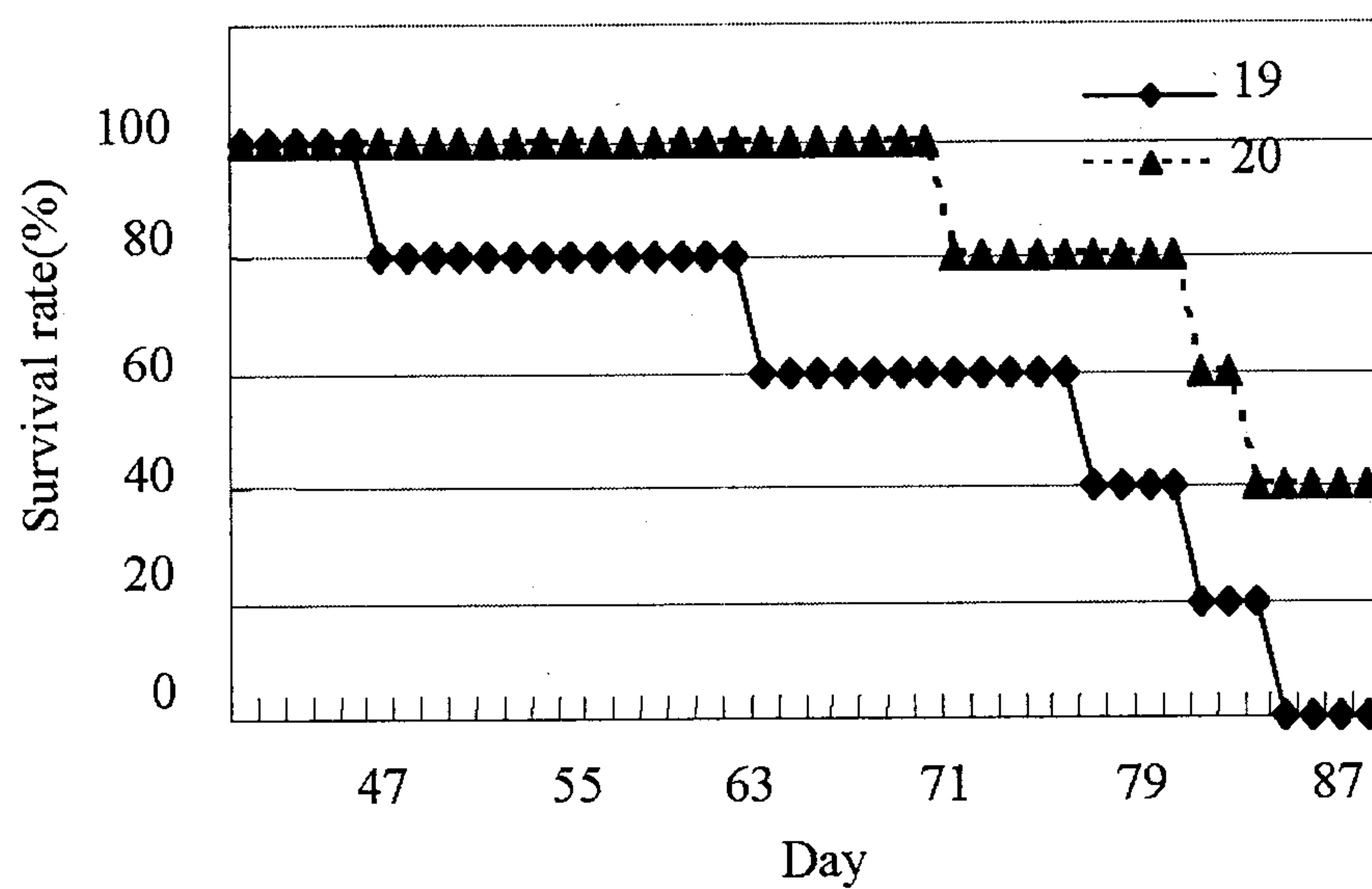


Fig.10

Survival rate (prophylactic model - colon cancer cell line)

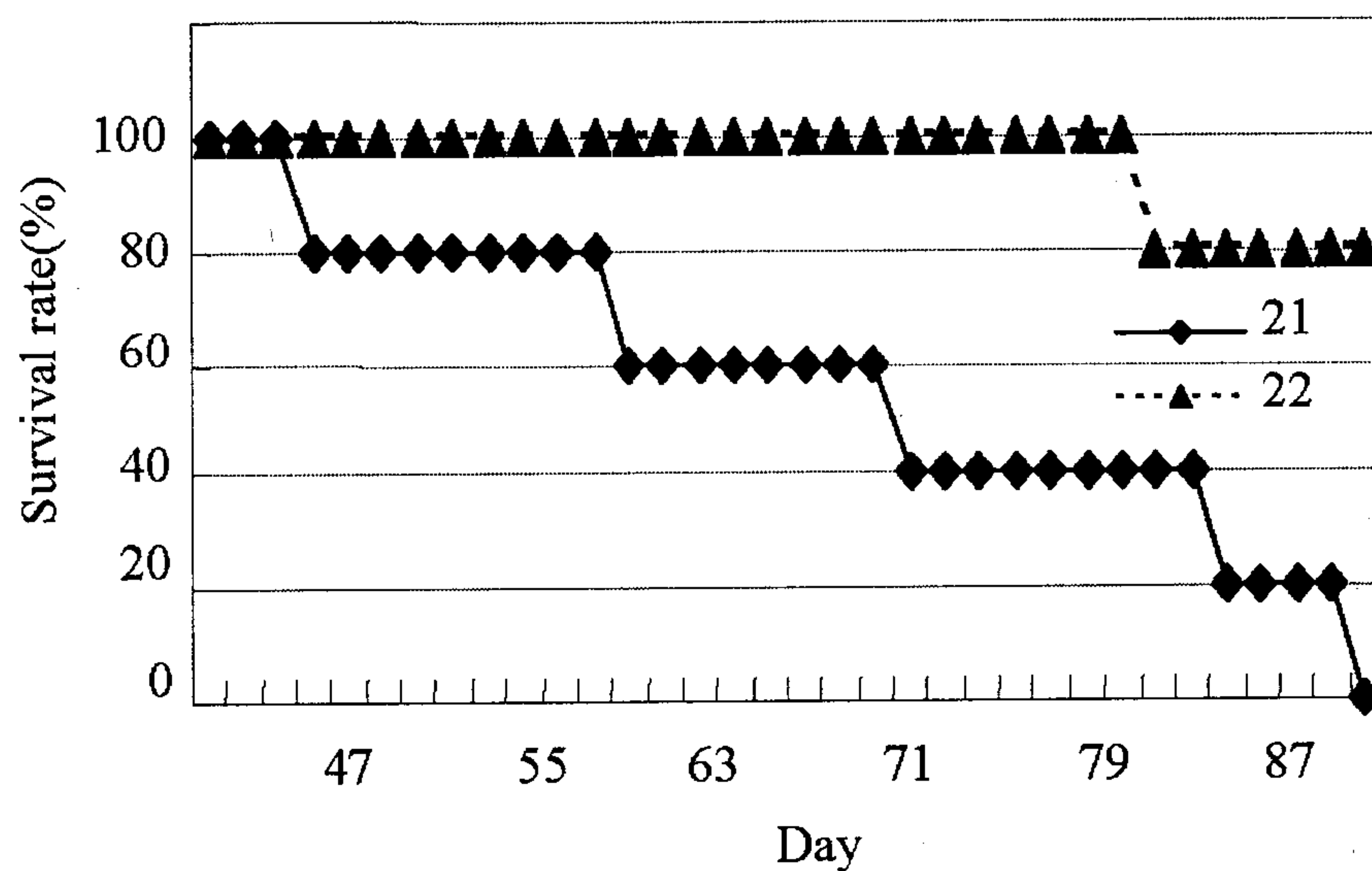


Fig.11

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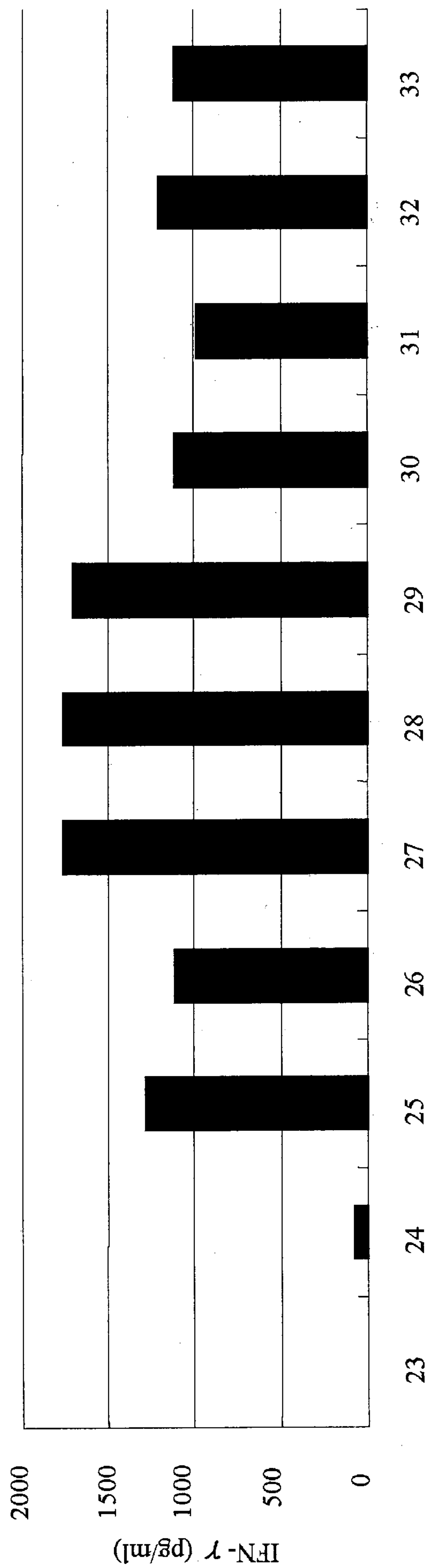


Fig.12

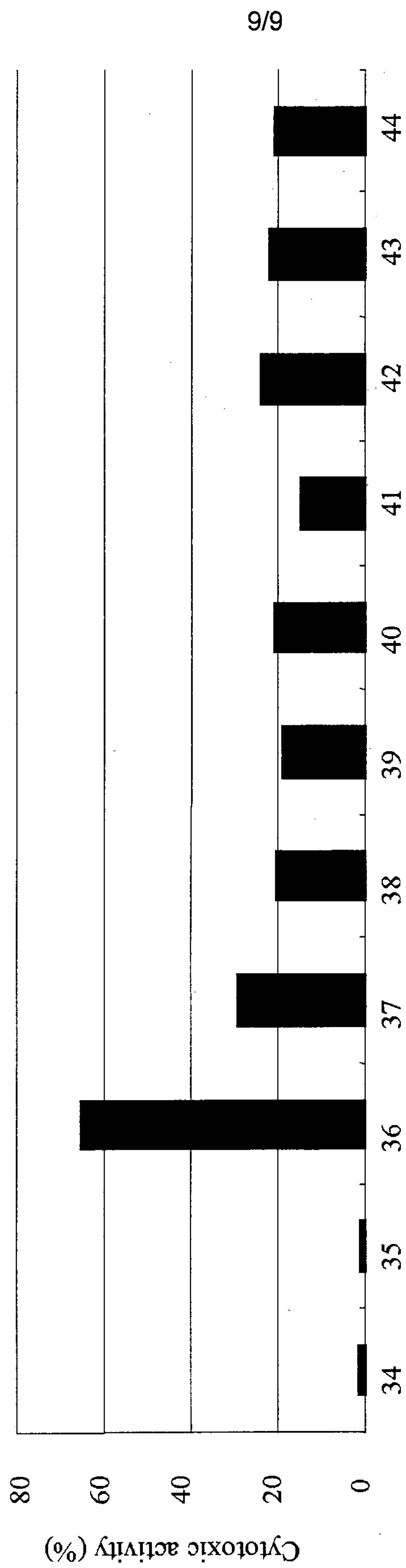


Fig.13