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(72) Inventeur/Inventor:

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(57) **Abrégé/Abstract:**

Tumor antigen inducing and/or activating HLA-A2-restricted tumor-specific cytotoxic T lymphocytes that is activated by recognizing HLA-A2 and a tumor antigen peptide, and a peptide or polypeptide derived from the tumor antigen, a polynucleotide encoding the peptide or a complementary strand polynucleotide thereof, a transformant comprising a recombinant vector which comprises the polynucleotide are provided.

(72) Inventeurs(suite)/Inventors(continued): ITOH, KYOGO, JP

(73) Propriétaires(suite)/Owners(continued): GREEN PEPTIDE CO., LTD, JP

(74) Agent: MOFFAT & CO.

Abstract of the disclosure

Tumor antigen inducing and/or activating HLA-A2-restricted tumor-specific cytotoxic T lymphocytes that is activated by recognizing HLA-A2 and a tumor antigen peptide, and a peptide or polypeptide derived from the tumor antigen, a polynucleotide encoding the peptide or a complementary strand polynucleotide thereof, a transformant comprising a recombinant vector which comprises the polynucleotide are provided.

DESCRIPTION

TUMOR-SPECIFIC T CELL ACTIVATION BY PEPTIDE ANTIGENSFIELD OF THE INVENTION

The present invention relates to a tumor antigen, and more particularly relates to a peptide or a polypeptide recognized by tumor-specific cytotoxic T lymphocytes, a polynucleotide encoding the peptide or the polypeptide and a complementary strand polynucleotide thereto, a recombinant vector comprising the polynucleotide, a transformant comprising the recombinant vector, an antibody against the peptide or the polypeptide, a compound having any interaction with the peptide or the polypeptide or the polynucleotide, a cytotoxic T lymphocyte inducer consisting of the peptide and/or the polypeptide, and a pharmaceutical composition comprising the same, and a method for producing the polypeptide, a method for screening for a compound having any interaction with the peptide or the polypeptide or the polynucleotide, a method for inducing cytotoxic T lymphocytes using the peptide or the polypeptide, a method for measuring the peptide or the polypeptide or the polynucleotide encoding the polypeptide, and a reagent kit used for the measuring method.

BACKGROUND OF THE INVENTION

The immune system, particularly cytotoxic T lymphocytes (which, hereinafter, may be abbreviated to CTLs) play an important role in the exclusion of cancer *in vivo*. Infiltration of cytotoxic T

lymphocytes exhibiting a cytotoxic activity against tumor cells has been detected at the tumor site of a cancer patient (Arch. Surg., 126:200-205, 1990.) A target molecule (tumor antigen) of the tumor-specific cytotoxic T lymphocytes was first discovered in a melanoma. A tumor antigen generated in a tumor cell is degraded in the cell into a peptide (tumor antigen peptide) consisting of 8 to 11 amino acids, which binds to a human leukocyte antigen (HLA) molecule that is the major histocompatibility complex antigen to be displayed on the surface of the tumor cell. The cytotoxic T lymphocytes recognize a complex consisting of HLA and the tumor antigen peptide, and damage the tumor cell. In other words, the cytotoxic T lymphocytes recognize the tumor antigen peptide in an HLA-restricted manner.

HLA is a cell membrane antigen, and is expressed on almost all eukaryotic cells. HLA is mainly classified into class I antigen and class II antigen. The HLA recognized by the cytotoxic T lymphocytes together with an antigen peptide belongs to class I antigens. HLA class I antigens are further classified into HLA-A, HLA-B, HLA-C, and so on. It was reported that HLA has genetic polymorphism. The HLA-A2 allele, which is one of polymorphisms of HLA-A subregion, is found in approximately 23% of African Blacks, approximately 53% of Chinese, approximately 40% of Japanese, approximately 49% of Northern Caucasians, and approximately 38% of Southern Caucasians.

As used herein, a tumor antigen means a protein, a polypeptide, or a peptide, which constitutes part of the tumor cell and is capable of inducing tumor-specific cytotoxic T lymphocytes. A tumor antigen peptide means a peptide that is generated as a result of degradation

of the tumor antigen in a tumor cell and can induce or activate tumor-specific cytotoxic T lymphocytes upon being expressed on the cell surface by binding to an HLA molecule. In addition, the site of the amino acid sequence which is capable of inducing tumor-specific cytotoxic T lymphocytes that is present in a tumor antigen is called a tumor antigen epitope (tumor antigen determinant.)

In recent years, many genes encoding tumor antigens that can be recognized by cytotoxic T lymphocytes have been identified from cDNA of human tumor cells (Science 254:1643-1647, 1991; J. Exp. Med. 183:1185-1192, 1996; J. Immunol. 163:4994-5004, 1999.) Some of these genes are involved in cellular proliferation and malignant transformation, including HER/neu (Proc. Natl Acad. Sci. USA, 92:432-436, 1995) mutant cdk (Science, 269:1281-1284, 1995) mutant CASP-8 (J. Exp. Med., 186:785-793, 1997) and so on.

On the other hand, a molecule such as a tumor rejection antigen gene and a T cell antigen receptor (TCR), which are involved in specific immunity, have been identified in melanoma, esophageal cancer, and other cancers in the past 10 years, and a specific immunotherapy of advanced cancer or metastatic cancer has been studied using the peptide.

Now, in Europe and in the United States, cancer vaccine therapy has been developed in which cytotoxic T lymphocytes are activated by an administration of a tumor antigen in a cancer patient. Results from a clinical test of a melanoma specific tumor antigen have been reported. For example, administration of a melanoma antigen gp-100 peptide subcutaneously to melanoma patients along with administering interleukin-2 (IL-2) intravenously gave a tumor regression in 42%

of the patients (Nature Medicine, 4:321, 1998.) In this way, by utilizing a tumor antigen as a vaccine, an effective treatment against cancer can be achieved.

However, almost all of the identified tumor antigens are derived from melanomas. Tumor antigens derived from epithelial cancers and adenocarcinomas, such as pancreatic cancer, which occur at high incidence rates, have been reported for such specific immunotherapy only in a few papers. Pancreatic cancer is one of the largest causes of death by cancer in the world and causes about 27,000 deaths a year in the USA and about 50,000 deaths in Europe. The main factors causing these large numbers of deaths are lack of an effective therapeutic method, the difficulty of diagnosis, and the activity of this cancer. Only 1 to 4% of pancreatic cancer patients have overcome the disease, and the incidence substantially equals the death rate. Therefore, a new approach of therapy, for example, development of specific immunotherapy is needed.

In addition, in view of the diversity of cancer, an identical tumor antigen should not be expressed in the same degree in all cancer cells. Naturally, cancer vaccine therapy by activating the cytotoxic T lymphocytes using one kind of tumor antigen has a therapeutic effect on cancer having the tumor antigen. However, in order to induce and activate the tumor antigen-specific cytotoxic T lymphocytes and obtain a high therapeutic effect corresponding to the diversity of cancer, it is important to discover and use many novel tumor antigens in accordance with the diversity of cancer.

DISCLOSURE OF THE INVENTION

One embodiment of the present invention is a peptide consisting of an amino acid sequence according to any one of those from SEQ ID NO: 1 to SEQ ID NO: 44 in the sequence listing.

One embodiment of the present invention is a polypeptide consisting of an amino acid sequence according to any one of those from SEQ ID NO: 45 to SEQ ID NO: 53.

One embodiment of the present invention is a medicament comprising one or more of peptides or polypeptides selected from the peptides, which consist of the amino acid sequence according to any one of those from SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing, and the polypeptides, which consist of an amino acid sequence according to any one of those from SEQ ID NO:45 to SEQ ID NO:53 in the sequence listing.

One embodiment of the present invention is an anti-cancer vaccine comprising one or more of peptides or polypeptides selected from the peptides, which consist of the amino acid sequence according to any one of those from SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing, and the polypeptides, which consist of an amino acid sequence according to any one of those from SEQ ID NO:45 to SEQ ID NO:53.

One embodiment of the present invention is an anti-cancer vaccine comprising one or more of peptides or polypeptides selected from the peptides, which consist of the amino acid sequence according to any one of those from SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing, and the polypeptides, which consists of an amino acid sequence according to any one of those from SEQ ID NO:45 to SEQ ID NO:53 in the sequence listing, for use in the treatment of pancreatic cancer,

colon cancer, or stomach cancer.

One embodiment of the present invention is an inducer of cytotoxic T lymphocytes comprising one or more of peptides or polypeptides selected from the peptides, which consist of the amino acid sequence according to any one of those from SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing, and the polypeptides, which consist of an amino acid sequence according to any one of those from SEQ ID NO:45 to SEQ ID NO:53 in the sequence listing.

One embodiment of the present invention is a method for inducing cytotoxic T lymphocytes using one or more of peptides or polypeptides selected from the peptides, which consist of the amino acid sequence according to any one of those from SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing, and the polypeptides, which consist of an amino acid sequence according to any one of those from SEQ ID NO:45 to SEQ ID NO:53 in the sequence listing.

One embodiment of the present invention is a polynucleotide encoding a peptide or a polypeptide consisting of the amino acid sequence according to any one of those from SEQ ID NO:1 to SEQ ID NO:53 in the sequence listing, or the complementary strand thereof.

One embodiment of the present invention is a polynucleotide according to any one of those from SEQ ID NO:54 to SEQ ID NO:62 in the sequence listing, or the complementary strand thereof.

One embodiment of the present invention is a polynucleotide according to any one of those from SEQ ID NO:54 to SEQ ID NO:62 in the sequence listing, or the complementary strand thereof, wherein a polypeptide encoded by the polynucleotide induces cytotoxic T lymphocytes and/or is recognized by cytotoxic T lymphocytes.

One embodiment of the present invention is a polynucleotide that hybridizes to the polynucleotide or the complementary strand thereof under stringent conditions.

One embodiment of the present invention is a recombinant vector comprising the polynucleotide or the complementary strand thereof or the polynucleotide that hybridizes to the polynucleotide or the complementary strand thereof under stringent conditions.

One embodiment of the present invention is a recombinant expression vector comprising the polynucleotide or the complementary strand thereof or the polynucleotide that hybridizes to the polynucleotide or the complementary strand thereof under stringent conditions.

One embodiment of the present invention is a transformant transformed with the recombinant vector or the recombinant expression vector, which comprises the polynucleotide or the complementary strand thereof or the polynucleotide that hybridizes to the polynucleotide or the complementary strand thereof under stringent conditions.

One embodiment of the present invention is a method for producing the polypeptide, which comprises culturing the transformant transformed with the recombinant expression vector that comprises the polynucleotide or the complementary strand thereof or the polynucleotide that hybridizes to the polynucleotide or the complementary strand thereof under the stringent conditions.

One embodiment of the present invention is an antibody that immunologically recognizes the peptide or the polypeptide.

One embodiment of the present invention is a method for screening for a compound that enhances at least recognition of the peptide

or the polypeptide by HLA-A2-restricted cytotoxic T lymphocytes, by interacting with the peptide or the polypeptide and/or HLA-A2 to enhance, and/or the compound that enhances expression of the polynucleotide or the complementary strand thereof by interacting with the same, wherein the method uses at least one selected from a group consisting of the peptide, the polypeptide, the polynucleotide or the complementary strand thereof, the recombinant vector or the recombinant expression vector, the transformant, and the antibody.

One embodiment of the present invention is a compound obtained by the method for screening a compound that enhances at least recognition of the peptide or the polypeptide by HLA-A2-restricted cytotoxic T lymphocytes, by interacting with the peptide or the polypeptide and/or HLA-A2 to enhance, and/or the compound that enhances expression of the polynucleotide or the complementary strand thereof by interacting with the same, wherein the method uses at least one selected from a group consisting of the peptide, the polypeptide, the polynucleotide or the complementary strand thereof, the recombinant vector, the recombinant expression vector, the transformant, and the antibody.

One embodiment of the present invention is a compound that enhances recognition of at least one of the peptide or the polypeptide by the HLA-A2-restricted cytotoxic T lymphocytes, or the compound that enhances the expression of the polynucleotide or the complementary strand thereof by interacting with the same.

One embodiment of the present invention is a pharmaceutical composition used for cancer treatment, comprising at least one selected from a group consisting of the peptide, the polypeptide,

the polynucleotide or the complementary strand thereof, the recombinant vector or the recombinant expression vector, the transformant, the antibody, and the compound.

One embodiment of the present invention is use of the medicament, the anti-cancer vaccine, the inducer of the cytotoxic T lymphocytes, or the pharmaceutical composition for cancer disease.

One embodiment of the present invention is a method for measuring quantitatively or qualitatively the peptide or the polypeptide, or the polynucleotide.

One embodiment of the present invention is a reagent kit used in the method for measuring quantitatively or qualitatively the peptide or the polypeptide, or the polynucleotide, wherein the kit comprises at least one selected from a group consisting of the peptide, the polypeptide, the polynucleotide or the strain thereof, and the antibody.

One embodiment of the present invention is use of a reagent kit for a test of the cancer disease, wherein the kit is used to measuring quantitatively or qualitatively the peptide or the polypeptide, or the polynucleotide, comprises at least one selected from a group consisting of the peptide, the polypeptide, the polynucleotide or the complementary strain thereof, and the antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates that OK-CTLp (HLA-A0207/A3101) lyses tumor cells in an HLA-A2-restricted manner.

Fig. 2 illustrates that recognition of the human pancreatic adenocarcinoma cell line Panc-1 by OK-CTLp and interferon- γ production

as a result thereof is an HLA-A2-restricted event.

Fig. 3 illustrates that OK-CTLp recognizes COS7 cells, in which each of cDNA clones 1 to 6 ((A) in the figure) and cDNA clone 7 ((B) in the figure), obtained from the human pancreatic adenocarcinoma cell line Panc-1, was coexpressed with HLA-A2, in an HLA-A2-restricted manner.

Fig. 4 illustrates that cDNA clones 1 to 6, obtained from the human pancreatic adenocarcinoma cell line Panc-1, are recognized by OK-CTLp in a dose-dependent manner. In the figure, (A), (B), (C), (D), (E), and (F) each show that OK-CTLp recognizes COS7 cells, in which each of cDNA clones 1 to 6, having high homology with UBE2V, HNRPL, WHSC2, EIF4EBP1, ppMAPkkk, and 2-5 OAS3, respectively, was coexpressed with HLA-A2, in an HLA-A2-restricted manner. The symbol —■— shows the amount of interferon- γ produced by OK-CTLp, when the HLA-A0207 gene was coexpressed with the each tumor antigen gene in target cells, —◇— shows the amount of interferon- γ produced by OK-CTLp, when the HLA-A2402 gene was coexpressed with each tumor antigen gene in the target cells.

Fig. 5 illustrates that OK-CTLp or OK-CTL clone recognizes five peptides derived from a gene product of the tumor antigen gene 1 that is obtained from the human pancreatic adenocarcinoma cell line Panc-1, which has high homology with UBE2V.

Fig. 6 illustrates that OK-CTLp or OK-CTL clone recognizes four peptides derived from a gene product of the tumor antigen gene 2 that is obtained from the human pancreatic adenocarcinoma cell line Panc-1, which has high homology with HNRPL.

Fig. 7 illustrates that OK-CTLp or OK-CTL clone recognizes

four peptides derived from a gene product of the tumor antigen gene 3 that is obtained from the human pancreatic adenocarcinoma cell line Panc-1, which has high homology with WHSC2.

Fig. 8 illustrates that OK-CTLp or OK-CTL clone recognizes two peptides derived from a gene product of the tumor antigen gene 4 that is obtained from the human pancreatic adenocarcinoma cell line Panc-1, which has high homology with EIF4EBP1.

Fig. 9 illustrates that OK-CTLp or OK-CTL clone recognizes three peptides derived from a gene product of the tumor antigen gene 5 that is obtained from the human pancreatic adenocarcinoma cell line Panc-1, which has high homology with ppMAPkkk.

Fig. 10 illustrates that OK-CTLp or OK-CTL clone recognizes one peptide derived from a gene product of the tumor antigen gene 6 that is obtained from the human pancreatic adenocarcinoma cell line Panc-1, which has high homology with 2-5 OAS3.

Fig. 11 illustrates representative peptides showing that the tumor antigen peptides, which are derived from products of the tumor antigen genes obtained from the human pancreatic adenocarcinoma cell line Panc-1, are recognized by OK-CTL clone in a dose-dependent manner. Each of (A), (B), (C), (D), (E), and (F) in this figure shows that OK-CTLp recognizes the peptides which are derived from gene products of the tumor antigen genes 1 to 6, having high homology with UBE2V, HNRPL, WHSC2, EIF4EBP1, ppMAPkkk, and 2-5 OAS3, respectively.

Fig. 12 illustrates that three peptides derived from a gene product of the tumor antigen gene 1 having high homology with UBE2V can induce CTL showing cytotoxicity against HLA-A2⁺ tumor cell from peripheral blood mononuclear cells of a cancer patient. The symbol

—■— shows the human pancreatic adenocarcinoma cell line Panc-1 (HLA-A0201/1101,) —◆— shows the human colon adenocarcinoma cell line SW620 (HLA-A0201/2402,) —○— shows the HLA-A2⁻ lung adenocarcinoma cell line RERF-LC-MS (HLA-A1101/1101,) —△— shows an EBV transformed autologous B cell (HLA-A0207/3101,) and —□— shows a PHA blast of autologous T cell (HLA-A0207/3101.) These symbols are also used in the same manner in Figs. 13 to 17 described below.

Fig. 13 illustrates that two peptides derived from a gene product of the tumor antigen gene 2 having high homology with HNRPL can induce CTL showing cytotoxicity against HLA-A2⁺ tumor cell, from peripheral blood mononuclear cells of a cancer patient.

Fig. 14 illustrates that two peptides derived from a gene product of the tumor antigen gene 3 having high homology with WHSC2 can induce CTL showing cytotoxicity against HLA-A2⁺ tumor cell, from peripheral blood mononuclear cells of a cancer patient.

Fig. 15 illustrates that two peptides derived from a gene product of the tumor antigen gene 4 having high homology with EIF4EBP1 can induce CTL showing cytotoxicity against HLA-A2⁺ tumor cell, from peripheral blood mononuclear cells of a cancer patient.

Fig. 16 illustrates that one peptide derived from a gene product of the tumor antigen gene 5 having high homology with ppMAPkkk can induce CTL showing cytotoxicity against HLA-A2⁺ tumor cell, from peripheral blood mononuclear cells of a cancer patient.

Fig. 17 illustrates that one peptide derived from a gene product of the tumor antigen gene 6 having high homology with 2-5 OAS3 can induce CTL showing cytotoxicity against HLA-A2⁺ tumor cell, from peripheral blood mononuclear cells of a cancer patient.

Fig. 18 illustrates that tumor antigen peptides can induce CTL, which shows cytotoxic activity in an HLA-A2-restricted manner and in a dose-dependent manner, from peripheral blood mononuclear cells of a cancer patient. (A), (B), (C), (D), and (E) in this figure each show that peptides derived from gene products of the tumor antigen genes 1 to 5, having high homology with UBE2V, HNRPL, WHSC2, EIF4EBP1, and ppMAPkkk, respectively, induces CTL that recognizes the peptide in a HLA-A2-restricted manner, from peripheral blood mononuclear cells of a cancer patient. The symbol —■— shows T2 cells in which the tumor antigen peptide was made to express and —◇— shows autologous PHA blastoid T cells.

Fig. 19 illustrates that gene products of the tumor antigen genes KM-PA-2 ((A) in the figure) and KM-PA-4 ((B) in the figure), which were obtained from the human pancreatic adenocarcinoma cell line CFPAC-1, are recognized by OK-CTLp in an HLA-A2-restricted manner.

Fig. 20 shows that peptides derived from the tumor antigen genes KM-PA-2 and KM-PA-4, respectively, which were obtained from the human pancreatic adenocarcinoma cell line CFPAC-1 (A and B in the figure, respectively), can induce CTL from peripheral blood mononuclear cells (PBMC) of a cancer patient, which shows cytotoxicity against T2 cells which have been pulsed with the peptide corresponding to the peptide used for stimulating the PBMC (left-hand figures of A and B in the figure,) and an HLA-A2⁺ tumor cell Panc-1 (right-hand of A and B in the figure).

Fig. 21 shows that CTL, which was induced from peripheral blood mononuclear cells of a cancer patient by peptide derived from the

tumor antigen gene KM-PA-2 obtained from the human pancreatic adenocarcinoma cell line CFPAC-1, lyses tumor cells in an HLA-A2-restricted manner.

BEST MODE FOR CARRYING OUT THE INVENTION

In order to identify a tumor rejection antigen gene and a tumor antigen encoded by the gene, which can be used for specific immunotherapy for pancreatic cancer, HLA-A2-restricted tumor-specific cytotoxic T lymphocytes have been established in the present invention that are activated by recognizing HLA-A2 and a tumor antigen peptide (hereafter, this cell may be called OK-CTLp) from a colon cancer patient, and genes encoding tumor antigens, which can be recognized by these tumor-specific cytotoxic T lymphocytes (CTL,) have been isolated/identified from a cDNA library of Panc-1 cell that as the human pancreatic adenocarcinoma cell line using the gene expression cloning method. In the present invention, genes have also been identified, which can be recognized by CTL in the same way as described above, from genes identified as those encoding the tumor antigen by the SEREX (Serological analysis of recombinant cDNA expression libraries) method (Proc. Natl Acad. Sci. USA, 92:11910-11813, 1995.) In addition, based on the tumor antigen encoded by the gene obtained, a peptide having the tumor antigen epitope has been found in the present invention.

As used herein, a polypeptide means a long chain peptide of arbitrary peptides comprising two or more amino acids bound to each other by a peptide bond or by a modified peptide bond. For example, a protein is included in the definition of polypeptide herein.

Moreover, a short chain peptide sometimes called an oligopeptide or an oligomer is simply called a peptide herein.

"Recognize" herein means that a subject distinguishes an object from others and cognates it, for example, binds to the object cognized. Particularly, in the present invention, CTL which recognize the tumor cells or the tumor antigen peptides means that CTL binds through a T cell receptor to the tumor antigen peptides that are presented by HLA.

"Activate" herein means to enhance or to make it work further a thing or a state, which has an activity or an action. Particularly, in the present invention, activation of CTL means that CTL recognizes an antigen being presented by HLA to produce IFN- γ or CTL shows cytotoxicity against the target cells recognized by CTL.

"Induce" herein means to generate an activity or an action from a thing or a state that are in a phase merely having the activity or the action. Particularly, in the present invention, induction of an antigen-specific CTL means to make CTL, which specifically recognizes a certain antigen differentiate and/or proliferate *in vitro* or *in vivo*. In addition, the inducer of cytotoxic T lymphocytes in the present invention means a medicament which changes the state, where CD8-positive T lymphocytes specifically recognizing a certain antigen is absent or present in a very low degree, to the state, where the cytotoxic T lymphocytes recognizing the antigen is present in a very degree.

(Isolation and identification of the tumor antigen gene, tumor antigen, and tumor antigen peptide)

In the present invention, OK-CTLp that was HLA-A2-restricted cytotoxic T lymphocyte described above was used as an effector cell and tumor antigens capable of activating this cell were isolated and identified by using the gene expression cloning method. In other words, cDNA of the human pancreatic adenocarcinoma cell line Panc-1 and cDNA of HLA-A0207 were cotransfected into COS-7 cells, and among those cells in which the transfected genes were expressed, the cells which enhance IFN- γ production from OK-CTLp were selected, and hence, the gene encoding the tumor antigen capable of activating CTL was identified. The method will be presented in more detail in examples described herein. As a result, seven cDNA clones were obtained which were recognized by OK-CTLp in an HLA-A2-restricted manner.

In addition, two genes, KM-PA-2 and KM-PA-4, encoding tumor antigens capable of activating CTL in an HLA-A2-restricted manner were found in the same manner as described above from the genes encoding the tumor antigens, were detected from a cDNA library of the human pancreatic adenocarcinoma cell line CFPAC-1 using the SEREX method and already reported (Biochim. Biophys. Res. Commun., 281:936-944, 2001,). The SEREX method is a method that can be applied to detection of a tumor antigen. However, among 1500 or more kinds of tumor antigens detected by this method, those being identified as tumor antigens capable of inducing both cell-mediated immunity and humoral immunity are only MAGE-1, tyrosinase, and NY-ESO-1. Thus, the tumor antigen identified by the SEREX method cannot always activate CTL. The present invention first revealed that the tumor antigen genes described above, KM-PA-2 and KM-PA-4, can activate CTL in an HLA-A2-restricted manner.

All seven cDNA clones described above, which were obtained

from Panc-1 cell, contained a complete open reading frame (ORF). The nucleotide base sequence of these genes was determined by the Sanger method (Chain Terminator method) to estimate the amino acid sequence on the basis of the nucleotide base sequence. When a homology search was carried out for these nucleotide base sequences and deduced amino acid sequences in an existing database such as GenBank™, it was found that these genes were cDNAs whose nucleotide base sequences are novel, though they have high homology with genes as described below. There is no report on the known homologous genes functioning as a tumor antigen. With regard to clone 3 among the 7 cDNA clones (clones 1 to 7) obtained, the sequence of an initial clone, which was obtained by the gene expression cloning method described above, and has high homology with that of a gene of Wolf - Hirschhorn syndrome candidate 2 protein (WHSC2), was 25 bp shorter at the 5'-terminal region than that of WHSC2, so that full-length cDNA was obtained from the cDNA library of the Panc-1 cell by a standard colony hybridization method using the clone labeled with ³²P as a probe. Hereinafter, the genes of the Panc-1 cell, from which the above-described clones 1 to 7 were derived, will be called gene 1 to 7, respectively. Also, the polypeptides consisting of an amino acid sequence encoded by each gene are occasionally herein called gene product 1 to 7. Deduced amino acid sequences encoded by each of these genes are shown as SEQ ID NO:45 to SEQ ID NO:51 in the sequence listing, respectively, and the nucleotide base sequences thereof are shown as SEQ ID NO:54 to SEQ ID NO:60 in the sequence listing, respectively. The above described genes 1 to 6 and the gene 7 were registered at the DNA Data Bank of Japan (DDBJ) of the National Research

Institute of Genetics in June 12th, 2000 and August 2nd, 2000, respectively (Table 1).

For KM-PA-2 and KM-PA-4, the homologous genes have been reported as shown in Table 1 (Biochem. Biophys. Res. Commun., 281:936-944, 2001.) The nucleotide base sequences of KM-PA-2 and KM-PA-4 are shown as SEQ ID NO:52 and SEQ ID NO:53 in the sequence listing, respectively, and the deduced amino acid sequences are shown as SEQ ID NO:61 and SEQ ID NO:62 in the sequence listing, respectively.

Table 1.

cDNA clone (gene)			Polypeptide encoded by cDNA			Homologous gene
	Base length (bp) [DDBJ accession no.]	SEQ ID:NO		Amino acid length	SEQ ID:NO	[GenBank accession no.]
1	1775 [AB044550]	54	PP 1	270	45	ubiquitin-conjugated enzyme variant Kua (UBE2V) [AF155120]
2	2097 [AB044547]	55	PP 2	589	46	heterogeneous nuclear ribonucleoprotein L (HNRPL) [NM_001533]
3	2243 [AB044549]	56	PP 3	549	47	Wolf-Hirschhorn Syndrome candidate 2 protein (WHSC2) [AK001304]
4	831 [AB044548]	57	PP 4	118	48	eIF-4E-binding protein 1 (EIF4EBP1) [NM_004095]
5	2404 [AB044546]	58	PP 5	779	49	partial putative mitogen activated protein kinase kinase kinase (ppMAPKKK) [AJ242724]
6	6707 [AB044545]	59	PP 6	1087	50	2',5'-oligoadenylate synthetase 3 (2-5 OAS3) [NM_006187]
7	769 [AB046744]	60	PP 7	216	51	cleavage and polyadenylation specificity factor (CPSF) [U37012]
KM-PA-2	2060 [AB060694]	61	PP-KM-PA-2	634	52	KIAA0124 gene [D50914] human homologue of mouse block of proliferatin 1 (Bop1) [BC005160]
KM-PA-4	1841	62	PP-KM-PA-4	142	53	coactosin-like protein (CLP) [L54057]

The nucleotide base sequence of gene 1 has high homology with that of the ubiquitin-conjugated enzyme variant Kua gene (UBE 2V)

registered at GenBank (accession no.AF155120.) The length of the deduced amino acid (aa) encoded by gene 1 was slightly longer than that encoded by the UBE2V gene (3 aa in positions 109 to 111.) The function of UBE2V has not so far been reported.

The nucleotide base sequence of gene 2 has high homology with that of the heterogeneous nuclear ribonucleoprotein L (HNRPL) gene (accession no.NM_001533.) However, the deduced amino acid length was slightly longer than that of the HNRPL gene at the N-terminal positions 1 to 31. The HNRPL gene product is a heterogeneous nuclear ribonucleoprotein complex and provides a substrate for the processing events that the mRNA precursor undergoes in the cytoplasm.

The nucleotide base sequence of gene 3 has high homology with that of the Wolf-Hirschhorn syndrome candidate 2 proteins (WHSC2) gene registered at GenBank (accession no.AK001304.) The WHSC2 gene seems to have some functions in the phenotype of WHS, a multiple malformation syndrome characterized by mental and developmental defects resulting from a partial deletion of the short arm of chromosome 4.

The nucleotide base sequence of gene 4 has high homology with that of the eIF-4E-binding protein 1 gene (EIF4EBP1, accession no.NM_004095.) The product of EIF4EBP1 gene is known as a translation initiation factor that initiates insulin-dependent phosphorylation of 4E-BP1, making it available to form an active cap-binding complex.

The nucleotide base sequence of gene 5 has homology with that of the partial putative mitogen-activated protein kinase kinase kinase gene (ppMAPKKK, accession no.AJ242724) registered at GenBank. The deduced amino acid sequence encoded by gene 5 is 230 aa longer at

the N-terminal and 258 aa longer at the C-terminal as compared with that of the registered ppMAPkkk gene (its function has not yet been reported.)

The nucleotide base sequence of gene 6 consists of 6707 bp and has homology with that of the 2',5'- oligoadenylate synthetase 3 gene (2-5 OAS3 gene, accession no.NM_006187) with a total of 13-aa differences at positions 18, 159, 249, 287, 288, 316, 393 to 398, and 984. 2-5 OAS3 is known as an IFN-induced protein that plays an important role in immune-protection against microorganism infection.

The nucleotide base sequence of gene 7 has homology with positions 3701 to 4463 of the Human cleavage and polyadenylation specificity factor (CPSF, accession no.U37012) gene and the amino acid sequence is approximately 1226 aa shorter.

The nucleotide base sequence of gene KM-PA-2 has high homology with that of the KIAA0124 and human homologues of mouse block of proliferation 1 (Bop1.) The nucleotide base at position 1466 of the KIAA0124 gene is guanine (G) and thus, the amino acid residue of the 465th position is histidine (H). On the contrary, in gene KM-PA-2, they are adenine (A) and arginine (R), respectively.

The nucleotide base sequence of gene KM-PA-4 and the amino acid sequence encoded by the gene are identical to those of coactosin-like protein (CLP.)

In order to obtain tumor antigen peptides from the above-described 9 genes encoding a tumor antigen, peptides were designed and synthesized based on the amino acid sequences encoded by the above-described genes. For gene 7, the gene was regarded as a part of a gene consisting of a longer base sequence, so that the

peptides, which were derived from the amino acid sequence encoded by the gene (CPSF) homologous to gene 7, were also designed and synthesized. It has been known that a tumor antigen peptide capable of binding to the HLA-A2 has a motif (a specific sequence) in its sequence. Then, at first, the peptide having an HLA-A2 binding motif (a specific sequence) was searched for in the literature (J. Immunol., 152:163, 1994; Immunogenetics, 41:178, 1994,) and the peptides of 9-mer to 11-mer, which were different from each other and suited to the motif obtained, were designed and synthesized based on the amino acid sequence encoded by the above described genes. Recognition of each peptide by CTL was measured using OK-CTLp or several kinds of OK-CTL clones obtained by cloning OK-CTLp by the limiting dilution method using IFN- γ production from these CTL as an indicator. The OK-CTL clones are the cells recognizing any one of the above-described genes 1 to 7. On the other hand, OK-CTLp recognizes any of genes 1 to 7. The results revealed that OK-CTLp is a cell population recognizing various kinds of tumor antigens. Therefore, when the OK-CTL clones were used to test the peptide for its ability to activate CTL, a clone was used which recognizes the product of the gene encoding the same peptide as that to be tested. Forty four peptides (SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing; Table 2 and Table 3) among those synthesized were recognized by OK-CTLp or OK-CTL clones and enhanced IFN- γ production from CTL. Among these peptides, P1 to P5, P6 to P9, P10 to P13, P14 and P15, P16 to P18, and P19 are the peptides consisting of a partial sequence of the amino acid sequences encoded by gene 1, gene 2, gene 3, gene 4, gene 5, and gene 6, respectively, and encoded also by genes UBE2V, HNRPL, WHSC2,

EIF4-EBP1, ppMAPkkk, and 2-5 OAS3 having high homology with each genes. On the other hand, P25, P26, P27, P28, P30, and P31 are the peptides consisting of a partial sequence of the amino acid sequences encoded by gene 7 and gene CPSF having high homology with gene 7. P20, P21, P22, P23, P24, P29, and P32 consist of a partial sequence of the amino acid sequence specific to CPSF.

Table 2.

Number	Origin of peptide	Position of amino acid sequence	Amino acid sequence	SEQ ID NO: in sequence listing
P 1	Gene 1 (UBE2V)	43 - 51	RLQEWCSVI	1
P 2		64 - 73	LLLLARWEDT	2
P 3		85 - 93	LIADFLSGL	3
P 4		201 - 209	LLQDWHVIL	4
P 5		208 - 216	ILPRKHHRI	5
P 6	Gene 2 (HNRPL)	140 - 148	ALVEFEDVL	6
P 7		404 - 412	CLYGNVEKV	7
P 8		443 - 451	FMFGQKINV	8
P 9		501 - 510	NVLHFFNAPL	9
P10	Gene 3 (WHSC2)	103 - 111	ASLDSDEWV	10
P11		141 - 149	ILGELREKV	11
P12		157 - 165	MLPLECQYL	12
P13		267 - 275	TLLRKERGV	13
P14	Gene 4 (EIF4EBP1)	51 - 59	RITYDRKEL	14
P15		52 - 60	IITYDRKELM	15
P16	Gene 5 (ppMAPkkk)	290 - 298	QILKGLLFL	16
P17		294 - 302	GLLFLHIRT	17
P18		432 - 440	DLLSHAFFA	18
P19	Gene 6 (2-5 OAS3)	666 - 674	QQLCVYWIV	19
P20	CPSF	285 - 293	SLLYLNQSV	20
P21	CPSF	250 - 258	KVHPVIWSL	21
P22	CPSF	534 - 542	DMWTVIAPV	22
P23	CPSF	882 - 890	QLGQGNLKV	23
P24	CPSF	392 - 400	LLLKYTEKL	24
P25	Gene 7	1367 - 1375	TMLPHHAGL	25
P26	Gene 7	1296 - 1304	LLRRADFHV	26
P27	Gene 7	1401 - 1409	ELINRYLYL	27
P28	Gene 7	1358 - 1366	LIMLQNALT	28
P29	CPSF	797 - 805	YQLPDWRLV	29
P30	Gene 7	1359 - 1368	IMLQNALTIM	30
P31	Gene 7	1358 - 1367	LIMLQNALTT	31
P32	CPSF	456 - 465	TQLATYSFEV	32

Table 3.

Number	Origin of peptide	Position of amino acid sequence	Amino acid sequence	SEQ ID NO: in sequence listing
P 33	KM-PA-2	29 - 38	LEWYDDFPHV	33
P 34		115 - 124	FSGDVMIHPV	34
P 35		172 - 180	WAQEDPNAV	35
P 36		179 - 188	AVLGRHKMHV	36
P 37		326 - 335	RLWEVATARC	37
P 38		348 - 356	VAWNPSPAV	38
P 39		585 - 593	DLLQNPLL	39
P 40		586 - 595	LLQNPLLVPV	40
P 41		612 - 621	VIFHPTQPWV	41
P 42	KM-PA-4	15 - 24	NLVRDDGSAV	42
P 43		57 - 65	RLFAFVRFT	43
P 44		104 - 113	VVQNFAKEFV	44

These tumor antigen peptides are presented on a cell surface by HLA-A2 and recognized by T cell receptor (TCR) expressed on the peptide-specific OK-CTL clone. The peptides derived from gene 1 and UBE2V, gene 2 and HNRPL, or gene 6 and 2-5 OAS3 are recognized by OK-CTL clone expressing TCR-V β 8.1, TCR-V β 3.2, or TCR-V β 14. In addition, Peptides derived from gene 3 and WHSC2, gene 4 and EIF4EBP1, or gene 5 and ppMAPkkk are recognized by OK-CTL clone expressing TCR-V β 13, TCR-V β 8.1, or TCR-V β 18, respectively.

Two each of the OK-CTL clones that recognize peptides derived from gene 1 and UBE2V, gene 2 and HNRPL, and gene 6 and 2-5 OAS3 were expressed TCR possessing different complementarity-determining regions 3 (CDR 3; an element responsible for binding to antigenic epitopes on a groove of the HLA Class I molecules,) respectively. The OK-CTL clone recognizing peptides derived from gene 3 and WHSC2, gene 4 and EIF4EBP1, and gene 5 and ppMAPkkk also expressed TCR

possessing the different CDR3, respectively.

Moreover, the above-described 44 peptides recognized by OK-CTLp each induced HLA-A2-restricted tumor-specific CTL *in vitro* from the peripheral blood mononuclear cells (which, hereinafter, may be abbreviated to PBMC) which are autologous cells derived from a colon cancer patient from whom OK-CTLp was obtained, and/or from the PBMC of HLA-A0201⁺ cancer patients (pancreatic cancer, colon cancer, and stomach cancer.) The above-described CTL induced from the peripheral blood mononuclear cells of the cancer patients lysed HLA-A2⁺ tumor cells in a dose-dependent manner. However, no lysis was observed in the HLA-A2⁻ tumor cell RERF-LC-MS, and HLA-A⁺ autologous EBV-B cells and HLA-A⁺ T cells stimulated by PHA, both of which are derived from normal cells. In addition, the above-described CTL showed cytotoxicity in a dose-dependent manner against the T2 cells that were pulsed with the same peptide as that used for stimulation.

On the basis of the examination described above, 44 tumor antigen peptides capable of activating OK-CTLp were obtained. Furthermore, it was found that these peptides could induce HLA-A2-restricted tumor-specific CTLs from PBMC derived from patients of pancreatic cancer, colon cancer, and/or stomach cancer. In addition, it was revealed that both the pancreatic adenocarcinoma cell line Panc-1 and the colon adenocarcinoma cell line SW620 are recognized by CTLp and by CTLs induced from PBMC by the above described peptide. This result suggests that pancreatic cancer and colon cancer have a common tumor antigen epitope recognized by host CTLs.

(Polypeptide and peptide)

A polypeptide according to the present invention is a polypeptide consisting of the amino acid sequence each of which is encoded by the above described genes 1 to 7 obtained from the human pancreatic adenocarcinoma cell line Panc-1 or gene KM-PA-2 or KM-PA-4 obtained from the human pancreatic adenocarcinoma cell line CFPAC-1, and preferably, a polypeptide consisting of the amino acid sequence described in any one of those from SEQ ID NO:45 to SEQ ID NO:53 in the sequence listing. These polypeptides can be used for inducing and/or activating CTL as a tumor antigen. Moreover, these polypeptides can be used as a material for specifying a tumor antigen epitope to obtain a tumor antigen peptide.

A peptide according to the present invention can be obtained by designing peptides, for example, which are suited for the HLA-A2-restricted motif, based on the amino acid sequence of the above-described polypeptide, to select ones recognized by CTL, for example, which activate and/or induce CTL, from the designed peptides. A peptide according to the present invention may be the peptide having a property of a tumor antigen epitope presented on the surface of an antigen-presenting cell through binding to HLA-A2 and recognized by CTL. The peptide consists of amino acid residues of at least about 5 or more, preferably about 7 or more, and more preferably 9 to 10. Particularly preferably, the peptide is one consisting of an amino acid sequence described in any one of those from SEQ ID NO:1 to SEQ ID NO:44 in the sequence listing. These peptides can be used as a tumor antigen peptide for activating and/or inducing the HLA-A2-restricted tumor-specific cytotoxic T lymphocytes.

For activating and/or inducing CTL, one of the above-described

polypeptide or peptide may be used or they may be used in combination of two or more. As described above, CTL is a population consisting of plural cells that recognize various antigens, so that it is recommended to use these peptides preferably in combination of two or more.

A polypeptide or peptide, which has one or several amino acid(s) with a mutation such as deletion, substitution, addition, or insertion introduced into the polypeptide or peptide specified as above and is recognized by at least the HLA-A2-restricted CTL, is also included within the scope of the present invention. A means for introducing mutations such as a deletion, substitution, addition, or insertion is well known and, for example, Ulmer's technique (Science, 219:666, 1983) can be employed. When introducing such mutation, in view of preventing a change of the fundamental properties (such as the physical properties, activity, or immunological activity) of the peptide, mutual substitution among, for example, amino acids having similar properties (polar amino acids, non-polar amino acids, hydrophobic amino acids, hydrophilic amino acids, positively charged amino acids, negatively charged amino acids, aromatic amino acids, and so on) can be carried out. In addition, some modification can be made on these peptides to such an extent that there is no notable change of their function, such as modification of the constitutive amino group or carboxyl group.

(Polynucleotide)

A polynucleotide according to the present invention is a polynucleotide consisting of the nucleotide base sequence described

in any one of those from SEQ ID NO:54 to SEQ ID NO:62 in the sequence listing, which are the nucleotide base sequences of genes 1 to 7 or gene KM-PA-2 or KM-PA-4 obtained from the human pancreatic adenocarcinoma cell line Panc-1 or the human pancreatic adenocarcinoma cell line CFPAC-1 as described above, or the complementary strand thereof. The polynucleotide may also be a polynucleotide encoding each of the peptides consisting of the amino acid sequences described in any one of those from SEQ ID NO:1 to SEQ ID NO:44 or a polypeptide consisting of the amino acid sequence described in any one of SEQ ID NO:45 to SEQ ID NO:53 in the sequence listing, or the complementary strand thereof. Moreover, the above-described polynucleotide may consist of a nucleotide base sequence of at least about 15 or more, preferably about 21 to 30 or more nucleotides, wherein the nucleotide base sequence corresponds to a region encoding a tumor antigen epitope in the amino acid sequence of the polypeptides according to the present invention, or the complementary strand thereof. Selection of a useful polynucleotide and determination of its nucleotide base sequence are possible, for example, by employing well-known protein expression systems to confirm the ability of the expressed protein to induce and/or activate CTL.

Moreover, a polynucleotide that hybridizes to the above-described polynucleotide under stringent conditions is included in the scope of the present invention. In the case where the polynucleotide molecule is a DNA molecule, "a DNA molecule that hybridizes to a DNA molecule under stringent conditions" can be obtained, for example, by the method described in "Molecular Cloning: A Laboratory Manual (Cold Spring Harbor Laboratory, 1989.)" "To

hybridize under stringent conditions" herein means that a positive hybridizing signal is still observed even under the condition in which, for example, incubation is carried out in a solution containing 6 X SSC, 0.5% SDS, and 50% formamide at 42°C and then, washing is carried out in a solution containing 0.1 X SSC and 0.5% SDS at 68°C.

The above-described polynucleotide can induce and/or activate the HLA-A2-restricted CTL, when it is expressed in cells having HLA-A2. In this case, the above-described polynucleotide has a poly(A) structure in its 3'-terminal. The number of poly(A) does not have an influence on the site encoding the amino acid acting as a tumor antigen, so that the number of poly(A,) of the polynucleotide is not limited.

All of the above-described polynucleotides provide genetic information useful for producing a polypeptide or a peptide according to the present invention or can be also utilized as a reagent and a standard of a nucleic acid.

(Recombinant vector)

A recombinant vector can be obtained by inserting the above-described polynucleotide into an adequate DNA vector. The DNA vector used is properly selected in accordance with the kind of host and the purpose of use. The DNA vector may be a naturally existing one and also may be one that lacks a part of its DNA other than that necessary for replication. For example, vectors can be exemplified as those derived from a chromosome, an episome, and a virus, for example, vectors derived from a bacterial plasmid, derived from a bacteriophage, derived from a transposon, derived from an enzyme

episome, derived from an inserting element, and derived from an enzyme chromosome element, for example, vectors derived from a virus such as baculovirus, papovavirus, SV40, vacciniavirus, adenovirus, fowlpox virus, pseudorabies virus, and retrovirus, and vectors prepared by combination of them, for example, vectors derived from the genetic element of the plasmid and the bacteriophage, for example, a cosmid and a phagemid. Further, an expression vector and a cloning vector etc. can be used in accordance with the desired purpose.

The recombinant vector, which comprises the constitutional elements of the desired DNA sequence and a DNA sequence possessing information relating to replication and regulation, such as a promoter, a ribosome-binding site, a terminator, a signal sequence, an enhancer, and so on, can be prepared by combining them using well-known methods. As a method for inserting the polynucleotide according to the present invention into the above-described DNA vector, the well-known methods can be employed. For example, a method can be used, wherein an appropriate restriction enzyme is chosen for treating a DNA to cleave it at a specific site, and then, the DNA is mixed with the DNA used as a vector treated in the same way, followed by ligating with a ligase. A desired recombinant vector can also be obtained by ligating an adequate linker to the desired polynucleotide followed by inserting the resultant molecule into a multi-cloning site of a vector suitable for a purpose.

(Transformant)

The DNA vector in which the above-described polynucleotide has been inserted can be used to obtain a transformant by transforming

a well-known host such as *Escherichia coli*, yeast, *Bacillus subtilis*, an insect cell, or a mammalian cell therewith by well-known methods. In the case of carrying out the transformation, a more preferable system is exemplified by the method for integrating the gene in the chromosome, in view of achieving stability of the gene. However, an autonomous replication system using a plasmid can be conveniently used. Introduction of the DNA vector into the host cell can be carried out by standard methods such that described in "Molecular Cloning: A Laboratory Manual" (ed. by Sambrook et al., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989.) Concretely, calciumphosphate transfection, DEAE-dextran™-mediated transfection, microinjection, cation lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction and infection can be employed.

(Producing polypeptide or peptide)

Using an expression vector as a DNA vector for transduction of the above-described transformant, a polypeptide or a peptide according to the present invention can be provided. A transformant, transformed with a DNA expression vector comprising the above-described polynucleotide, is cultured under well-known culture conditions suitable for each host. Culturing may be conducted by using indicators, such as a function of the polypeptide or a peptide according to the present invention that is expressed by the transformant, particularly at least the activity to induce and/or activate CTL, or the peptide or the amount of the peptide produced in the host or outside of the host. Subculturing or batch culturing

may be also carried out using an amount of the transformant in the culture as an indicator.

A peptide according to the present invention can be produced by a general method known in peptide chemistry. For example, "Peptide Synthesis (Maruzen) 1975" and "Peptide Synthesis, Interscience, New York, 1996" are exemplified. However, any widely known method can be used.

A polypeptide or peptide according to the present invention can be purified and collected by a method, such as a gel filtration chromatography, an ion column chromatography, an affinity chromatography, and the like, in combination, or by fractionation means on the basis of a difference in solubility using ammonium sulfate, alcohol, and the like, using a CTL-activating ability of the polypeptide or the peptide as an indicator. More preferably used is a method, wherein the polypeptide or the peptides are specifically adsorbed and collected by using polyclonal antibodies or monoclonal antibodies, which are prepared against the polypeptide or the peptides based on the information of their amino acid sequences.

(Antibody)

An antibody according to the present invention is prepared by using the above-described polypeptide or peptide as an antigen. An antigen may be the above-described polypeptide or peptide itself, or its fragment that is composed of at least 5, more preferably at least 8 to 10 amino acids. In order to prepare the antibody specific to the above-described polypeptide or peptide, a region consisting of the amino acid sequence intrinsic to the above-described

polypeptide or peptide is desirably used. The amino acid sequence is not necessarily homologous to the amino acid sequence of the polypeptide or the peptide, but is preferably a site exposed to outside of a stereo-structure of the polypeptide or the peptide. In such a case, it is sufficient that the amino acid sequence of the exposed site is consecutive in the exposed site, even if it may be discrete in its primary structure. The antibody is not limited as long as it binds or recognizes the polypeptide or the peptide immunologically. The presence or absence of the binding or the recognition can be determined by a well-known antigen-antibody binding reaction.

In order to produce an antibody, a well-known method for antibody production can be employed. For example, the antibody is obtained by administration of the polypeptide or peptide according to the present invention to an animal in the presence or absence of an adjuvant with or without linking such to a carrier so as to induce humoral immunity and/or cell-mediated immunity. Any carrier can be used as long as it is not harmful to the host. For example, cellulose, a polymerized amino acid, albumin, and the like are exemplified, but not limited thereto. As an animal used for immunization, a mouse, rat, rabbit, goat, horse, and so on, is preferably used.

A polyclonal antibody can be obtained from serum of an animal subjected to the above-described immunological means by a well-known method for collecting antibodies. A preferable means is exemplified by immunoaffinity chromatography.

A monoclonal antibody can be produced by collecting antibody-producing cells (for example, a lymphocyte derived from a spleen or a lymph node) from the animal subjected to the

above-described immunological means, followed by introducing a well-known transformation means with a permanently proliferating cell (for example, myeloma strain such as P3/X63 - Ag8 cells.) For example, the antibody-producing cells are fused with the permanent proliferating cells by a well-known method to prepare hybridomas. Then, the hybridomas are subjected to cloning, followed by selecting ones producing the antibody that recognizes specifically the above-described polypeptide or peptide to collect the antibody from a culture solution of the hybridoma.

The polyclonal antibody or the monoclonal antibody thus obtained, which recognizes and binds to the above-described polypeptide or peptide, can be utilized as an antibody for purification, a reagent, a labeling marker and so on.

(Screening and compound obtained by screening)

The above-described polypeptide or peptide, the polynucleotide encoding the same and the complementary strand thereof, the cell transformed based on the information concerning the amino acid sequence and nucleotide base sequence, or the antibody immunologically recognizing the same provide an effective means for screening a substance capable of inducing and/or activating CTL, when using them solely or in combination with each other. The screening method can be constructed utilizing a well-known screening system. For example, as shown in Examples herein, using a system in which the activation of CTL by the antigen-presenting cells that are pulsed with the tumor antigen peptide, is measured on the basis of the amount of IFN- γ production from CTL. Addition of a test substance to the system allows

one to select the substance inducing and/or activating CTL and the substance enhancing the induction and/or the activation. This system describes one screening method, but the screening method according to the present invention is not limited thereto.

A compound obtained by the above-described screening method is also part of the present invention. The compound may be a compound enhancing the recognition of the polypeptide or the peptide by CTL through an interaction with the polypeptide or the peptide according to the present invention, and/or HLA-A2. Further, it may be a compound enhancing the expression of the polynucleotide according to the present invention through an interaction with the polynucleotide. The compound thus selected can be used in a pharmaceutical composition by selecting ones having both biological usefulness and low toxicity.

(Pharmaceutical composition)

The polypeptide or peptide according to the present invention can be used for activating and/or inducing the HLA-A2-restricted tumor-specific cytotoxic T lymphocytes, as a tumor antigen or a tumor antigen peptide. In other words, the method for inducing CTL, which is characterized in that the above-described polypeptide or peptide is used, and a inducer of CTL comprising the above-described polypeptide or peptide are included in the scope of the present invention.

The polypeptide or the peptide according to the present invention, the polynucleotide encoding the polypeptide and the complementary strand thereof, the recombinant vector prepared based on the information of their amino acid sequences and nucleotide base

sequences, the cell transformed with the recombinant vector, or the antibody immunologically recognizing the polypeptide or the peptide, the compound enhancing the recognition of the polypeptide or the peptide by CTL through interaction with the polypeptide or the peptide, and/or HLA-A2, or the compound enhancing expression of the polynucleotide through interaction therewith can be used as a pharmaceutical composition comprising at least one species thereof, when using them solely or in combination with each other.

Concretely, for example, medicament consisting of the polypeptide or the peptide according to the present invention, and the pharmaceutical composition comprising the polypeptide or the peptide according to the present invention can be used as a so-called anti-cancer vaccine. In such a case, in order to activate the cell-mediated immunity, the polypeptide or the peptide according to the present invention can be used in the presence or absence of an adjuvant with or without linking such to a carrier. Any carrier can be used as long as it is not harmful to the human body. For example, cellulose, a polymerized amino acid, or albumin is exemplified, but the carrier is not limited thereto. A dosage form is properly chosen from those to which the well-known means for preparing a polypeptide or a peptide are applied. The amount thereof to be administered depends on a degree of recognition of the peptide by CTL, and is generally 0.01 mg to 100 mg/day/adult human body, preferably 0.1 mg to 10 mg/day/adult human body as an amount of active substance. Such an amount is administered once every several days or every several months.

Alternately, an effective action of an anti-cancer vaccine can also be obtained by collecting a mononuclear cell fraction from

the peripheral blood of a patient, and culturing the fraction with a peptide according to the present invention, followed by returning the mononuclear cell fraction, in which CTL are induced and/of activated, back into the blood of the patient. Culture conditions, such as the concentration of mononuclear cells and the concentration of the polypeptide or the peptide according to the present invention when they are cultured, can be readily determined. Further, a substance, such as interleukin 2 (IL-2) having an ability to induce the growth of lymphocytes may be added to the culture.

In the case of using the polypeptide or the peptide according to the present invention as an anti-cancer vaccine, using even only one polypeptide or one peptide is effective as an anti-cancer vaccine. However, plural kinds of the above-described polypeptide or peptide can be used in combination. CTL of the cancer patient is the population of cells recognizing various tumor antigens, so that using plural kinds of polypeptides or peptides as an anti-cancer vaccine may give a higher effect than using only one kind.

The above-described medicament, inducer of the cytotoxic T lymphocytes, anti-cancer vaccine and pharmaceutical composition are useful for treatment of a cancer disease such as pancreatic cancer, colon cancer, or stomach cancer.

In addition, the polynucleotide encoding the polypeptide according to the present invention and the complementary strand thereof are also useful for gene therapy of a cancer disease such as pancreatic cancer, colon cancer, or stomach cancer.

A method in which these polynucleotides are present in a vector and directly introduced *in vivo*, and a method in which cells are

collected from a donor followed by introducing polynucleotides present in a vector in vitro, can be both utilized. Retrovirus, adenovirus, and vaccinia virus exemplify the vectors, and retrovirus-related ones are preferred. Needless to say, these viruses show deficiency for replication. The amount of administration thereof can depend on the degree of recognition by CTL of the polypeptide encoded by the polynucleotide. Generally, as a DNA content encoding the tumor antigen peptide according to the present invention, the amount ranges from 0.1 μ g to 100 mg/day/adult human body, preferably 1 μ g to 50 mg/day/adult human body. This amount is administered once every several days or every several months.

(Measuring method for diagnosis and reagent)

The polypeptide or the peptide according to the present invention, the polynucleotide encoding the polypeptide and the complementary strand thereof, and the antibody immunologically recognizing the polypeptide or the peptide can be used independently for a diagnostic marker and a reagent etc. The present invention also provides a reagent kit comprising one or more containers in which one or more species thereof are present. For the preparation thereof, it is sufficient to use a well-known means for their preparation according to each of polypeptide or peptide, polynucleotide, or antibody.

Diagnostic means for a disease related to expression or activity of the polypeptide or the peptide according to the present invention can be carried out, for example, utilizing the interaction or reactivity with the polynucleotide encoding the polypeptide, by

determining the existing amount of the corresponding nucleic acid molecule, and/or determining a distribution of the polypeptide or the peptide in an individual living body, and/or determining a presence of the polypeptide or the peptide, and the existing amount in a sample derived from the individual body. In other words, measurement is carried out quantitatively or qualitatively for the polypeptide or the peptide according to the present invention or the polynucleotide encoding the same as the diagnostic marker. As a method for quantitative or qualitative measurement of the polypeptide or the peptide or the nucleic acid encoding the same, which are present in the sample, a well-known method can be utilized. Radioimmunoassay, competitive binding assay, Western blotting analysis, ELISA, and the like exemplify such a method. In addition, the nucleic acid molecule can be detected and quantified at an RNA level by using, for example, amplification, polymerase chain reaction (PCR,) RT-PCR, RNase protection, Northern blotting method, and other hybridization methods.

The sample subjected to measurement is exemplified by the cells derived from an individual human body present in for example, blood, urine, saliva, spinal fluid, tissue biopsy, or autopsy material, and the like. The nucleic acid molecule subjected to measurement is obtained from the each sample described above by a well-known method for nucleic acid preparation. For the nucleic acid molecule, genomic DNA can be directly used for detection, or it may be enzymatically amplified by using PCR or any other amplification method before the analysis. RNA or cDNA may be similarly used. In comparing with a normal genotype, a deletion or insertion can be detected in

accordance with a size change of an amplification product. Hybridizing the amplified DNA with the labeled DNA encoding the above-described polypeptide can identify point mutations.

Detecting mutation of, reduction of, and increase in the polypeptide according to the present invention and the DNA encoding the polypeptide by the above-described measuring method, makes it possible to diagnose diseases, to which the polypeptide is associated, such as pancreatic cancer, colon cancer, or stomach cancer.

EXAMPLES

The present invention will be illustrated more concretely with the following examples, but is not limited thereto.

Example 1

(Establishment of HLA-A2-restricted CTL)

The HLA-A2-restricted tumor-specific cytotoxic T lymphocyte line was established from tumor infiltrating lymphocytes (TIL) of a colon tumor patient (HLA-A0207/3101, HLA-B46/51, HLA-Cw1) (Int. J. CANCER, 81:459-466, 1999; J. Immunol., 163:4994-5004, 1999.) Specifically, TIL obtained from the colon tumor patient was cultured for a long period up to 50 days or longer by adding 100 U/ml of recombinant human interleukin 2 (IL-2.) Every 7 days, a portion of TIL activated by IL-2 was collected and cultured together with various kinds of tumor cells or normal cells to assay its CTL activity by measuring the produced IFN- γ and by measuring ^{51}Cr released from the cancer cells (J. Immunol., 163:4994-5004, 1999.) IFN- γ was measured by an enzyme-linked immunosorbent assay (ELISA). At day 58 after the start

of the culture, OK-CTLp, which is one of sublines showing HLA-A2-restricted tumor-specific CTL activity, was obtained. OK-CTLp obtained is a cell population in which 80% of the cells have a phenotype of $CD3^+CD4^-CD8^+$ and 20% of the cells have a phenotype of $CD3^+CD4^+CD8^-$. Using OK-CTLp as an effector cell and culturing it together with various kinds of cells that are used as a target cell, such as a tumor cell, the cytotoxicity to the target cell and activation of OK-CTLp were measured using the ^{51}Cr -release test and by using IFN- γ production as an indicator, respectively. The results are each presented in Fig. 1 and Fig. 2.

OK-CTLp obtained, as shown in Figs. 1 and 2, recognized HLA-A0201 $^+$ Panc-1 pancreatic adenocarcinoma cell, SW620 colon adenocarcinoma cell, HLA-A0206 $^+$ KE3 esophageal squamous-cell carcinoma (SCC) cell and HLA-A0207 $^+$ CA9-22 oral SCC cell to produce IFN- γ and represent sufficient cytotoxicity. However, no cytotoxicity was shown against HLA-A2 $^-$ tumor cells, such as QG56 lung adenocarcinoma cell, RERF-LC-MC lung adenocarcinoma cell, and COLO320 colon adenocarcinoma cell, and autologous Epstein-Barr virus transformed B cell (EBV-B) and autologous phytohemagglutinin (PHA)-blastoid T cells both derived from the normal cells. Further, OK-CTLp lysed all of the HLA-A2 $^+$ tumor cells tested (R27 breast cancer cell, HAK-2 primary hepatocellular carcinoma cell, SK-MEL-5 melanoma cell, and SF126 astrocytoma cell, which are HLA-A0201 $^+$, and HLA-A0206 $^+$ PC9 lung adenocarcinoma cell, and 1-87 lung adenocarcinoma cell and OMC-4 cervical SCC cell, which are HLA-A0207 $^+$.) The CTL activity was inhibited by an anti-HLA class I monoclonal antibody (mAb), an anti-CD8 mAb or an anti-HLA-A2 mAb, but not inhibited by other mAbs

(Fig. 2.) This result revealed that OK-CTLp recognizes the above-described tumor cells in a HLA-A2-restricted manner and shows cytotoxicity.

Meanwhile, the genotype of the HLA class I alleles of the above-described tumor cells has been disclosed (J. Immunol., 163:4994-5004, 1999.) The serotype of the HLA class I of the above-described patients was determined by applying a conventional method using the peripheral blood mononuclear cells (PBMC). In addition, the HLA-A2 subtype was determined by a sequence-specific oligonucleotide probe method and direct DNA sequencing. The phenotype of OK-CTLp was analyzed by direct immunofluorescence analysis using anti-CD3 mAb, anti-CD4 mAb, or anti-CD8 mAb (made by Nichirei) or anti-TCR $\alpha\beta$ mAb (WT31, Becton Dickinson), which were labeled with fluorescein isothiocyanate (FITC). In addition, the antibodies used to analyze for HLA-A2 restriction and specificity of OK-CTLp were anti-HLA class I mAb (W6/32, IgG2a,) anti-HLA-A2 mAb (BB7.2, IgG 2b,) anti-CD8 mAb (Nu-Ts/c, IgG2a,) anti-HLA class II mAb (H-DR-1, IgG2A,) and anti-CD4 mAb (Nu-Th/i, IgG1.) Anti-CD13 mAb (MCS-2, IgG2a) and Anti-CD14 mAb (JML-H14, IgG1) were used as an isotype-matching control mAb.

Example 2

(Isolation and identification of cDNA clone encoding tumor antigen)

A gene encoding the tumor antigen of the Panc-1 tumor cell recognized by OK-CTLp was isolated and identified according to the well-known gene expression cloning method (J. Immunol., 163:4994

-5004, 1999.) Specifically, poly(A)⁺ RNA of the Panc-1 tumor cells was converted to cDNA, and ligated with a SalI adapter so as to insert into the expression vector pCMV-SPORT-2 (Invitrogen Corp..)

cDNAs of HLA-A0207, HLA-A2402, or HLA-A2601 were obtained by reverse transcriptase polymerase chain reaction (RT-PCR) and cloned into the eukaryote expression vector pCR3 (Invitrogen Corp..)

200 ng of the above-described plasmid DNA pool or clones of Panc-1 cell cDNA library was mixed with 200 ng of the cDNA of HLA-A0207 in 100 μ l of Opti-MEM (Invitrogen Corp.) for 30 min. 50 μ l of this mixture was added to COS-7 cells (5×10^3) and incubated for 6 h in a 96-well U-bottom type microculture plate (Nunc Corp.) for co-transduction. Then, RPMI-1640 culture medium containing 10% FCS was added to and culturing was carried out for 2 days, followed by the addition of OK-CTLp (5×10^4) to each well. After a further 18 h incubation, 100 μ l of the supernatant was collected and IFN- γ production was measured thereon by ELISA. In this case, using COS-7 cells to which the gene had not been transfected as a target, IFN- γ production by OK-CTLp was examined and the value of IFN- γ produced was subtracted as a background from that of each measurement. As a result, seven cDNA clones were obtained, which enhanced IFN- γ production by OK-CTLp through recognition by OK-CTLp.

The nucleotide sequence of the seven cDNA clones obtained was determined by dideoxynucleotide sequencing method using a DNA sequencing kit (Perkin Elmer Corp.) and using an ABI PRISMTM377DNA sequencer (Perkin Elmer Corp.) In addition, the amino acid sequence encoded by each clone was deduced from the nucleotide base sequence. Also, a homology search of the nucleotide base sequence of these

clones was conducted through accessing GenBank. The results are presented in the above-described Table 1. With regard to clone 3 among the seven cDNA clones (clones 1 to 7) obtained, the sequence of an initial clone, which was obtained by the gene expression cloning method described above, was 25 bp shorter at the 5'-terminal region than that of WHSC2 showing high homology, so that full-length cDNA was obtained from the cDNA library of the Panc-1 cell by a standard colony hybridization method using the clone labeled with ^{32}P as a probe.

As shown in Figs. 3(A) and 3(B), clones 1 to 7 were each recognized by OK-CTLp to enhance IFN- γ production of OK-CTLp. However, OK-CTLp did not recognize COS-7 cells to which HLA-A0207 cDNA and the cDNA clone used as a negative control were cotransfected, or COS-7 cells to which any one of cDNA clones 1 to 7 and the cDNA of HLA-A2402 or HLA-A2601 were cotransfected, and did not show the IFN- γ production. When various concentrations of cDNA clones 1 to 6 were cotransfected into COS-7 cells together with 100 ng of HLA-A0207 cDNA or HLA-A2402 cDNA, IFN- γ production by OK-CTL was observed in a dose-dependent manner ((A) to (F) of Fig. 4.)

Expression of the mRNA of these genes was examined by Northern blotting analysis. The same expression pattern was observed except for gene 5. These genes are expressed commonly in the tumor cells and normal cells. However, expression levels in tumor cells such as Panc-1 cell, SW620 cell, and CA9-22 cell were significantly higher than that in normal cells, such as the T cell stimulated by PHA and a B cell transformed by Epstein-Barr virus (EBV-B). Expression of mRNA of gene 5 was barely detected under these experimental conditions.

The reason may be that expression of gene 5 is rare as proven by the fact that colony hybridization using clone 5 labeled with ^{32}P gives only 3 clones from an about 1×10^6 cDNA library.

Example 3

(Establishing OK-CTL clone)

Since CTL activated by recognizing the tumor antigen is a population of cells recognizing plural kinds of tumor antigens, the above-described OK-CTLp was subjected to cloning by limiting dilution culture (0.3, 0.5, 1, 2, and 4 cells/well) to obtain an OK-CTL clone (J. Immunol., 163:4994-5004, 1999.) These clones are those having CTL activity selected by culturing them together with COS-7 cells into which 100 ng/well of any one of the above-described seven cDNA clones and 100 ng/well of HLA-A0207 cDNA were cotransfected, or with the tumor cells, in a cell ratio of 1:1, and measuring IFN- γ production. Specifically, three hundred CTL clones were obtained from the parent line OK-CTLp by a limiting dilution culture. Eighty CTL clones among them had HLA-A2-restricted tumor-specific CTL activity and expressed the phenotype of $\text{CD3}^+ \text{CD4}^- \text{CD8}^+$ and $\text{TCR } \alpha\beta^+$. Among them, 2, 3, 1, 3, 2, and 4 CTL clones showed reactivity to the COS-7 cells expressing clone 1, clone 2, clone 3, clone 4, clone 5, and clone 6, respectively. In other words, it was revealed that the tumor antigen recognized by CTL differs in accordance with the CTL clones. Table 4 shows data of fifteen typical CTL clones. This suggested that OK-CTLp, i.e., CTL derived from the cancer patient, is a population of cells recognizing plural kinds of tumor antigens.

Table 4.

CTL clone	cDNA expressed in COS-7 cell together with HLA-A0207 cDNA							Panc-1
	clone 1 (UBE2V)	clone 2 (HNRPL)	clone 3 (WHSC2)	clone 4 (EIF4EBP1)	Clone 5 (ppMAPkkk)	clone 6 (2-5 OAS3)	no cDNA	
2-2-H3	<u>110</u>	0	0	0	0	0	0	340
2-1-H12	<u>134</u>	0	0	0	0	0	0	264
1-2-D7	0	<u>200</u>	0	0	0	0	0	235
1-2-D12	0	<u>>1000</u>	0	0	0	0	0	>1000
4-1-H8	0	<u>133</u>	0	0	0	0	0	84
4-2-A11	0	0	<u>100</u>	0	0	0	0	725
0.5-1-H12	0	0	0	<u>>1000</u>	0	0	0	>1000
0.5-1-D6	19	0	0	<u>118</u>	0	13	0	448
4-2-B3	0	0	0	<u>95</u>	0	0	0	100
2-1-F4	0	0	0	0	<u>>1000</u>	0	0	>1000
0.5-1-H2	0	0	0	0	<u>81</u>	0	0	122
0.5-1-D7	27	34	0	0	0	<u>110</u>	0	304
0.5-2-A4	0	0	0	0	0	<u>113</u>	0	>1000
1-2-D1	21	0	22	44	0	<u>61</u>	0	78
2-2-B4	0	0	0	0	0	<u>>1000</u>	0	>1000

Example 4

(Preparation of tumor antigen peptide
and its CTL-inducing activity)

In order to obtain the tumor antigen peptide derived from the seven tumor antigen genes, which were obtained in Example 2 and can induce CTL in a HLA-A2-restricted manner, a peptide having an HLA-A2 binding motif (a specific sequence) was searched for in the literature

(J. Immunol., 152:163, 1994; Immunogenetics, 41:178, 1994,) and peptides of 9-mer to 11-mer, which were different from each other and suited to the motif obtained, was designed and synthesized based on the amino acid sequence encoded by the above-described genes 1 to 7 and the amino acid sequence of UBE2V, HNRPL, WHSC2, EIF4EBP1, ppMAPkkk, 2-5 OAS3, and CPSF having high homology with these genes. The purity of the peptides obtained was each 70% or higher.

Binding activity of the peptide to the HLA-A0201 molecule was tested using a T2 cell mutant strain (Cancer Res., 54:1071-1076, 1994.) The T2 cell expresses the HLA-A2 molecule on a cell surface without binding to a peptide, because of deficiency of TAP. Specifically, the synthesized peptide (10 μ M) and the T2 cells were incubated at 26°C for 3 h and, subsequently, incubated in 5% CO₂ and 95% air at 37°C for 3 h. Thus, T2 cells, on whose surface the peptide was presented by HLA-A2, were obtained. The cells were incubated together with anti-HLA-A2 mAb (BB7.2) followed by staining with R-phycoerythrin linked F(ab')₂ rabbit anti-mouse immunoglobulin (Ig) (DAKO Corp..) Then, the expression pattern was analyzed by employing FACScan (Beckman Dickinson Corp.), which resulted in confirmation that HLA-A0201 molecules with the peptide were expressed on the cell surface.

In order to test for recognition of a peptide by CTL, the T2 cells previously pulsed with each peptide (10 μ M) was used as a target cell (T), and OK-CTLp or OK-CTL clone was used as an effector cell (E). The target cell and the effector cell were incubated for 18 h, the supernatant collected, followed by measuring IFN- γ contained in the supernatant by an ELISA. In the case where OK-CTLp was used

as the effector, an E/T ratio was set to 10:1. In the case where the OK-CTL clone was used, it was set to 2:1 to conduct the test. On the other hand, in case where the OK-CTL clone was used to test for the CTL activating ability of the peptide, the clone was used which recognized the gene product encoding the peptide being examined. Using IFN- γ production of OK-CTLp or OK-CTL clone against the T2 cells, which had not been pulsed with the peptide, as a background, subtraction was performed from each measurement value. The results were shown in Figs. 5 to 10. Fig. 5, Fig. 6, Fig. 7, Fig. 8, Fig. 9, and Fig. 10 each show the result of the peptide derived from gene 1 and UBE2V, gene 2 and HNRPL, gene 3 and WHSC2, gene 4 and EIF4EBP1, and gene 5 and ppMAPkkk, and gene 6 and 2-5 OAS3.

Moreover, the various concentrations of each peptide were used for incubation together with the T2 cells to examine the CTL clone-activating ability, resulting in finding that the CTL clone can be activated by each peptide in a dose-dependent manner. Representative examples of peptides derived from gene 1 and UBE2V, gene 2 and HNRPL, gene 3 and WHSC2, gene 4 and EIF4EBP1, gene 5 and ppMAPkkk, and gene 6 and 2-5 OAS3 were presented in (A), (B), (C), (D), (E) and (F) of Fig. 11, respectively. On the other hand, Table 5 shows peptides derived from gene 7 and CPSF. In Table 5, the peptide derived from EBV and the peptide derived from influenza virus are positive controls, which can activate CTL.

As the result of these experiments, it was revealed that the peptides shown in Table 2 described-above can activate OK-CTLp and/or OK-CTL clone to produce IFN- γ .

Table 5.

Peptide	IFN- γ production (pg/ml)			
	Concentration of peptide			
	0.1 μ M	1 μ M	10 μ M	50 μ M
Derived from influenza virus	0	93	693	35
Derived from EBV	119	390	371	117
P20	344	643	0	34
P21	428	501	81	195
P22	254	1027	431	407
P23	6360	0	345	160
P24	728	Detection limit or higher	103	2
P25	69	1569	25	122
P26	141	418	1239	0
P27	352	889	250	0
P28	898	Detection limit or higher	0	144
P29	0	Detection limit or higher	86	362
P30	88	7001	Detection limit or higher	Detection limit or higher
P31	443	Detection limit or higher	Detection limit or higher	314

Example 5

(CTL induction from peripheral blood mononuclear cells
derived from cancer patient by a peptide)

Among the peptides that were able to enhance IFN- γ production from the OK-CTLp or OK-CTL clone in Example 4, those from P1 to P19 were examined for their ability to induce CTL from peripheral blood mononuclear cells derived from a cancer patient. The method for inducing CTL by a peptide was according to the well-known method (J. Exp. Med., 187:277-288, 1998; Cancer Res., 59:4056-4063,

1999.) Specifically, autologous peripheral blood mononuclear cells (PBMC) derived from a cancer patient, from whom OK-CTLp was obtained, were incubated together with the peptide (10 μ M.) The cells were re-stimulated at day 10 and 14 after the start of culturing, using autologous PBMCs as an antigen presenting cell (APC) which were pulsed with 10 μ M of the same peptide for 2 h and exposed to irradiation (30 gray.) At day 21 after the start of culturing, the cells were collected to test for surface phenotype. In addition, the cells were examined for the recognition of various target cells, using IFN- γ production measured by ELISA when they were cultured together with the target cells as an indicator. As a target cells, SW620 cell, CA9-22 cell, and Panc-1 cell, which are the HLA-A2⁺ tumor cells, were used. The result was shown in Table 6.

Table 6.

Peptide	MFI	IFN- γ production (pg/ml) from peripheral blood mononuclear cells in recognition of various target cells					
		QG56 (HLA-A26 /26)	RERF-LC-MS (HLA-A11 /11)	COLO320 (HLA-A24 /24)	SW620 (HLA-A0201 /24)	CA9-22 (HLA-A0207 /24)	Panc-1 (HLA-A0201 /11)
P1	571	0	26	50	235	81	492
P2	607	0	0	5	53	0	0
P3	910	0	0	44	188	58	289
P4	1008	0	0	0	60	0	0
P5	637	0	0	38	500	96	638
P6	819	0	8	40	344	863	527
P7	783	0	0	0	344	0	54
P8	499	0	26	0	142	165	186
P9	832	0	27	0	194	98	339
P10	504	0	0	0	108	130	163
P11	1089	0	0	0	893	62	>1000
P12	780	0	0	40	46	0	197
P13	656	0	15	0	151	95	115
P14	591	0	0	0	112	184	265
P15	789	0	32	0	199	219	502
P16	887	0	0	0	0	147	113
P17	660	0	0	0	>1000	>1000	691
P18	657	29	0	0	>1000	70	>1000
P19	775	0	30	66	55	48	105
no Peptide	491	0	0	36	0	0	17

PBMC stimulated *in vitro* using P1, P3, P5, P6, P8, P9, P10, P11, P13, P14, P15, P17, or P18 among the 19 peptides recognized SW620 cells, CA9-22 cells and Panc-1 cells, which are the HLA-A2⁺ tumor cells, produced IFN- γ in a significant amount. However, the PBMC barely recognized the HLA-A2⁻ tumor cell. On the other hand,

P2, P4, P7, P12, and P16 also induced CTL recognizing any one of the HLA-A2⁺ tumor cells. PBMC stimulated by P19 recognized not only the tumor cells expressing HLA-A2, but also the tumor cells expressing other types of HLA. IFN- γ production from these CTL was inhibited by anti-HLA class I mAb, anti-CD8 mAb, or anti-HLA-A2 mAb, and not inhibited by other mAbs. In addition, when peripheral blood mononuclear cells (PBMC) were prepared from blood of two HLA-A0201⁺ patients (a colon cancer patient and a pancreatic cancer patient) to examine CTL induction by the peptides, the same result as above was obtained. In other words, it was found that the above-described peptides can induce HLA-A2-restricted CTL from the peripheral blood mononuclear cells of the patient.

Binding affinity of the peptides to HLA-A0201 molecule was expressed as a relative mean fluorescence intensity (MFI) of the HLA-A2 molecule. The MFI of positive and negative controls were 898 and 490, respectively. It can be supposed that binding affinity of a peptide to the HLA-A0201 molecule has no correlation with induction of CTL by the peptide.

Moreover, CTL-activating ability of these 19 peptides was directly examined in a ⁵¹Cr-releasing test using toxicity to the target cells as an indicator. Specifically, the above-described PBMC, in which CTL was induced, was further recultured to proliferate in the presence of autologous APC, IL-2, and a corresponding peptide. At about day 21 to 28 after the start of reculturing, PBMC was collected and cytotoxicity thereof was tested again by measuring IFN- γ and by a 6-h ⁵¹Cr-releasing test. The results were shown in Figs. 12 to 17. PBMC of the cancer patient, which was stimulated by these peptides,

lysed the HLA-A2⁺ tumor cells. However, the autologous EBV-B cells and the T cells stimulated by PHA, both of which were derived from normal cells and were expressing HLA-A2, and the HLA-A2⁻ tumor cell RERF-LC-MS, were not lysed. However, PBMC stimulated by peptides P14, P15, and P17 also showed cytotoxicity to the autologous EBV-B cells. Moreover, PBMC stimulated by P19 showed high cytotoxicity to the autologous EBV-B cells. In addition, PBMC stimulated by these peptides showed cytotoxicity to the T2 cells, which was pulsed with the same peptide as that used for stimulation of PBMC, in a dose dependent manner. Typical examples are shown in (A) to (E) of Fig. 18. From these above, it was found that the above-described peptides can induce CTL, which shows HLA-A2-restricted cytotoxicity, from the peripheral blood mononuclear cells of the cancer patient.

Example 6

(CTL induction from peripheral blood mononuclear
cell of patient by peptide)

For six peptides (P21, P22, P24, P26, P30, and P32) with a purity of 95% or higher among peptides from P20 to P32 derived from gene 7 and CPSF among the tumor antigen peptide obtained in Example 4, the activity to induce CTL *in vitro* from human peripheral blood mononuclear cells (PBMC) was examined using IFN- γ production as an indicator. PBMC used was prepared from each peripheral blood of sixteen HLA-A2-positive cancer patients (4 patients with pancreatic cancer, seven patients with stomach cancer, and 5 patients with colon cancer) and six healthy individuals. Specifically, 1×10^5 PBMC was added to each well of 96-well U-bottom type microculture plate (Nunc

Corp.) and incubated together with 10 μ M of each of the above-described peptides in 200 μ l culture medium. The culture medium consisted of 45% RPMI-1640, 45% AIM-V (Invitrogen Corp.,) 10% fetal calf serum (FCS), 100U/ml of human interleukin-2, and 0.1 μ M MEM nonessential amino acid solution (Invitrogen Corp.). At day 4 and day 7 after the start of culturing, half of the culture medium was removed and replaced with the above-described composition comprising each corresponding peptide. At day 10 after the start of culturing, the cells were collected and washed, followed by reacting with T2 cells, which were pulsed with each corresponding peptide, to measure the amount of IFN- γ produced.

Meanwhile, the above-described cells cultured for 10 days after stimulation by the peptide were further cultured for 10 days. The cytotoxicity of the obtained cells against the Panc-1 pancreatic adenocarcinoma cell (HLA-A2) was measured by the standard 6-h ^{51} Cr-releasing test in an E/T ratio of 10:1. The results obtained are presented as % specific lysis (table 7). Together with this step, cytotoxicity against SSTW-9 tumor cell as the HLA-A2⁻ tumor cell was measured to use as a background that was subtracted from the above-described result.

As a result, induction of HLA-A2-restricted CTL from PBMC by P21, P22, P23, P26, P30, and P32, which was specific to each peptide, was observed in patients of 31% (5/16,) 38% (6/16,) 25% (4/ 6,) 31% (5/16,) 44% (7/16,) and 7% (1/16) of the above-described sixteen patients, respectively. On the other hand, induction of CTL by P21 and P22 from the PBMC of healthy individuals was found in 50% (3/6) and 33% (2/6,) respectively. However, the other peptides did not

induce CTL from the PBMC of healthy individuals (Table 7). The above-described CTL induced from PBMC of the cancer patients by using the peptide showed cytotoxicity against Panc-1 pancreatic adenocarcinoma cell, and also SW620 colon adenocarcinoma cell (HLA-A2/A24) and KWS stomach adenocarcinoma cell (HLA-A2), both of which are the HLA-A2⁺ tumor cells. However, lysis was not observed in SSTW9 stomach adenocarcinoma cell (HLA-A24), which is the HLA-A2⁻ tumor cell, or the PHA-blastoid T cells or the EBV-B transformed B cells, both of which express HLA-A2 and are not the tumor cells. Recognition of the tumor cell by the above-described CTL was inhibited by anti-HLA class I mAb, anti-CD8 mAb, or anti-HLA -A2 mAb, and not inhibited by other mAb.

Table 7

Origin of PBMC		INF- γ production (pg/ml) / % specific lysis					
		P21	P22	P23	P26	P30	P32
pancreatic cancer patient	1	0	0	0	0	0	0
	2	7	38 / 37	41 / 53	35 / 36	12	12
	3	0	0	0	0	0	0
	4	543 / 12	8	72 / 10	77 / 20	73 / 11	0
stomach cancer patient	5	0	0	0	53 / 11	0	0
	6	0	0	0	0	0	0
	7	0	0	46 / 10	0	0	0
	8	5	0	0	11	146 / 18	0
	9	1500< / 27	0	0	8	92	0
	10	0	0	0	0	46 / 26	0
	11	136 / 18	0	0	0	0	0
coloncancer patient	12	0	92 / 28	71 / 18	0	0	57 / 18
	13	0	179	138 / 10	0	41 / 12	0
	14	66 / 11	80 / 19	48	0	33 / 10	0
	15	0	5	14	40 / 12	0	0
	16	140	0	0	45	68	4
healthy individuals	HD1	0	0	0	0	0	0
	HD2	0	0	13	0	0	0
	HD3	58	0	8	0	14	0
	HD4	5	0	6	0	0	0
	HD5	224	0	83	13	0	0
	HD6	97	14	45	0	0	0

Example 7

(Isolation and identification of cDNA
encoding tumor antigen)

From the genes encoding the tumor antigens (Biochim. Biophys. Res. Commun., 281:936-944, 2001), which were detected by the SEREX

(Serological Analysis of Recombinant cDNA Expression Libraries) method (Proc. Natl Acad. Sci. USA, 92:11910-11813, 1995) and already reported, two tumor antigen genes, KM-PA-2 and KM-PA-4, which can activate HLA-A2-restricted CTL, were found by using the same method as that of Example 2. Specifically, cDNA clones each encoding KM-PA-2, KM-PA-4, KM-PA-5, KM-PA-14, KM-PA-15, or KM-PA-18 were packaged in pBluescript™ vector, and digested by EcoRI and XhoI to insert into pCMV-SPORT2. These cDNAs in various concentrations were each coexpressed in COS-7 cells together with HLA-A0207 or HLA-A2402. Using the COS-7 cells as a target cell, incubation was performed together with OK-CTLp. As a result, COS-7 cells, to which KM-PA-2 or KM-PA-4 was cotransfected with HLA-A0207, induced IFN- γ production from OK-CTLp, in a dose dependent manner of the gene ((A) and (B) of Fig. 19.) The SEREX method is a method for detection of the tumor antigen. However, among 1500 or more kinds of tumor antigens detected by this method, those identified as tumor antigens capable of inducing both cell-mediated immunity and humoral immunity are only MAGE-1, tyrosinase, and NY-ESO-1. Therefore, even a gene identified by the SEREX method as encoding the tumor antigen cannot always activate CTL. It was first found that the above-described tumor antigen genes, KM-PA-2 and KM-PA-4, can activate CTL in an HLA-A2-restricted manner.

Example 8

(Preparation of tumor antigen and activity for inducing CTL from
PBMC of cancer patient)

In order to obtain the tumor antigen peptide derived from the

tumor antigen genes, KM-PA-2 and KM-PA-4, obtained from Example 7, different peptides of 9-mer or 10-mer were designed based on the amino acid sequences encoded by KM-PA-2 and KM-PA-4 and synthesized by a well-known method, in the same way as that in Example 4.

The ability of the synthesized peptide to induce CTL from the peripheral blood mononuclear cells of the colon cancer patient, from whom OK-CTLp was obtained, was examined in the same way as that in Example 6. As a result, as shown in (A) and (B) of Fig. 20, PBMC that was stimulated in vitro using any one of peptides P33 to P41 (SEQ ID NO:33 to SEQ ID NO:41) derived from KM-PA-2 and peptides P42 to P44 (SEQ ID NO:42 to SEQ ID NO:44) derived from KM-PA-4, produced IFN- γ through recognition of the T2 cells (left-hand figure of (A) and (B) of Fig. 20,) which were pulsed with the peptide corresponding to that used for stimulation of the PBMC, and the Panc-1 cell (right-hand figure of (A) and (B) of Fig. 20,) which is the HLA-A2⁺ tumor cell. However, the PBMC reacted merely to the HLA-A2⁻ tumor cell. As a result, it was revealed that any one of the above-described twelve peptides can induce the antigen specific CTL from PBMC of the cancer patient in an HLA-A2-restricted manner and that the induced CTL can recognize the above-described peptides to produce IFN- γ in an HLA-A2-restricted manner. In addition, cytotoxicity of these CTLs induced by the peptides was directly confirmed by the ⁵¹Cr-releasing test in the same way as that in Example 6. Fig. 21 shows a representative example of the result. As shown in Fig. 21, CTLs induced from PBMC of the cancer patient by P35, P39, or P40 lysed Panc-1 cells and YPK-3 cells, both of which are HLA-A2⁺ tumor cells. However, the HLA-A2⁻ tumor cell PaCa-2, the EBV-B cell line OKAB2, and the T cells stimulated

by PHA, was not lysed. In other words, it was revealed that the above-described peptides can induce CTL showing cytotoxicity from the peripheral blood mononuclear cells of the cancer patient in an HLA-A2-restricted manner. Further, CTL was also induced by the above-described peptides from PBMC obtained from the cancer patient, such as a pancreatic cancer patient, in addition to the colon cancer patient from whom OK-CTLp was obtained.

Example 9

In order to determine the phenotype of TCR expressed on the cell surface of the CTL clone recognizing the above-described peptide, total RNA of each clone was obtained from each 5×10^6 CTL clones, which were obtained in Example 3, using RNazolTMB (TEL-TEST Corp.) cDNA was prepared using the SuperScriptTM Preamplification System (Invitrogen Corp.) for first strand cDNA synthesis. Single stranded cDNA was amplified by polymerase chain reaction (PCR) using one of the 22 different V β primers (V β 1 to 20) and 3'C β primers. PCR was performed for 35 cycles, wherein 1 cycle comprised denaturation at 94°C for 1 min, annealing at 58°C for 2 min, and extension at 72°C for 3 min. The PCR product was inserted into plasmid pCR2 followed by transformation into *Escherichia coli* using the TA cloning system (Invitrogen Corp.), selection of colonies, and plasmid preparation for determining the cDNA sequence.

As the result, two each of CTL clones reacting with the peptides derived from UBE2V and gene 1, the peptide derived from HNRPL and gene 2, and the peptide derived from 2-5 OAS3 and gene 6, expressed

TCR-V β 8.1, TCR-V β 3.2, and TCR-V β 14, respectively. In addition, CTL clones recognizing the peptide derived from WHSC2 and gene 3, the peptide derived from EIF4EBP1 and gene 4, the peptide derived from ppMAPkkk and gene 5, expressed TCR-V β 13.1, TCR-V β 8.1, and TCR-V β 18, respectively (Table 8-1 and Table 8-2).

Two each of CTL clones recognizing the peptide derived from UBE2V and gene 1, the peptide derived from HNRPL and gene 2, and the peptide derived from 2-5 OAS3 and gene 6, expressed TCR possessing different complementarity-determining regions 3 (CDR3) (an element responsible for binding to the antigenic epitopes on the groove of the HLA class I molecules), respectively. CTL clones recognizing the peptide derived from WHSC2 and gene 3, the peptide derived from EIF4EBP1 and gene 4, the peptide derived from ppMAPkkk and gene 5, expressed TCR possessing different CDR3, respectively. The amino acid sequence of each CDR3 is that shown with an underline in Table 8-2.

Table 8-1

CTL clone	Epitopes	VB	DB	JB	CB
2-2-H3	UBE2V 43-51	8.1	2.1	2.3	2
2-1-H12	UBE2V 43-51	8.1	2.1	2.3	2
1-2-D7	HNRPL 140-148	3.2	1.1	2.7	2
1-2-D12	HNRPL 140-148	3.2	1.1	2.7	2
4-2-A11	WHSC2 103-111	13.1	2.1	2.7	2
4-2-B3	EIF4EBP1 51-59	8.1	1.1	1.1	1
0.5-1-H2	ppMAPkkk 432-440	18	1.1	1.1	1
1-2-D1	2-5 OAS3 666-674	14	2.1	2.3	2
2-2-B4	2-5 OAS3 666-674	14	2.1	2.3	2

Table 8-2

CTL clone	VB	DB *	CB
2-2-H3	IYFNNNVPIDDSGMPEDRFS AKMPNAS FSTLKIQPSEPRDS AVYFCAS	<u>SLGLAGGEQ</u> FFGPGTRLTVL	EDLKNVFPPE
2-1-H12	IYFNNNVPIDDSGMPEDRFS AKMPNAS FSTLKIQPSEPRDS AVYFCAS	<u>SLGLAGGEQ</u> FFGPGTRLTVL	EDLKNVFPPE
1-2-D7	VSREKKERFSLILESASTNQTSMYLCA S	<u>SLDRS</u> YEQYFGPGTRLTVT	EDLKNVFPPE
1-2-D12	VSREKKERFSLILESASTNQTSMYLCA S	<u>SLDRS</u> YEQYFGPGTRLTVT	EDLKNVFPPE
4-2-A11	QGEVPNGYNVSRSTTEDFPLRLLSAAP SQTSVYFCAS	<u>SYGGGSS</u> YEQYFGPGTRLTV T	EDLKNVFPPE
4-2-B3	IYFNNNVPIDDSGMPEDRFS AKMPNAS FSTLKIQPSEPRDS AVYFCAS	<u>SRVSGE</u> AFFGQGTRLTVV	EDLKNVFPPE
0.5-1-H2	DESGMPKERFSAEFPKEGPSILRIQQV VRGDSAAYFCAS	<u>SPTELDTE</u> AFFGQGTRLTVV	EDLKNVFPPE
1-2-D1	VSRKEKRNFLILES P SPNQTS LYFCA S	<u>GGSTD</u> TQYFGPGTRLTVL	EDLKNVFPPE
2-2-B4	VSRKEKRNFLILES P SPNQTS LYFCA S	<u>GGSTD</u> TQYFGPGTRLTVL	EDLKNVFPPE

INDUSTRIAL APPLICABILITY

According to the present invention, HLA-A2-restricted cytotoxic T lymphocytes can be induced, which makes it possible to achieve a specific immunotherapy for pancreatic cancer, colon cancer, and stomach cancer. HLA-A2 alleles are found in 23% of African Blacks, 53% of Chinese, 40% of Japanese, 49% of Northern Caucasians, and 38% of Southern Caucasians. Consequently, the present invention can be expected its great contribution to cancer therapy. Moreover, the present invention greatly contributes to fundamental research on the molecule related to recognition by T cells of a pancreatic cancer cell, a colon cancer cell, stomach cancer, and so on.

SEQUENCE LISTING

Applicant: ITOH, Kyogo

Title of Invention: Tumor antigen

Number of Sequences: 62

Priority Application No.: P2000-231814

Priority Country: Japan

Priority Filing Date: July 31, 2000

PCT Application No.: PCT/JP01/06526

PCT Filing Date: July 30, 2001

Software: PatentIn Ver. 2.1

Information for SEQ ID No: # 1

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 1

Arg Leu Glu Trp Cys Ser Val Ile
1 5

Information for SEQ ID No: # 2

SEQUENCE CHARACTERISTICS

Length: 10

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 2

Leu Leu Leu Leu Ala Arg Trp Glu Asp Thr
1 5 10

Information for SEQ ID No: # 3

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 3

Leu Ile Ala Asp Phe Leu Ser Gly Leu
1 5

Information for SEQ ID No: # 4

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 4

Leu Leu Gln Asp Trp His Val Ile Leu
1 5

Information for SEQ ID No: # 5

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 5

Ile Leu Pro Arg Lys His His Arg Ile
1 5

Information for SEQ ID No: # 6

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 6

Ala Leu Val Glu Phe Glu Asp Val Leu
1 5

Information for SEQ ID No: # 7

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 7

Cys Leu Tyr Gly Asn Val Glu Lys Val
1 5

Information for SEQ ID No: # 8

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2

restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 8
 Phe Met Phe Gly Gln Lys Leu Asn Val
 1 5

Information for SEQ ID No: # 9

SEQUENCE CHARACTERISTICS

Length: 10

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 9
 Asn Val Leu His Phe Phe Asn Ala Pro Leu
 1 5 10

Information for SEQ ID No: # 10

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 10
 Ala Ser Leu Asp Ser Asp Pro Trp Val
 1 5

Information for SEQ ID No: # 11

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 11
 Ile Leu Gly Glu Leu Arg Glu Lys Val
 1 5

Information for SEQ ID No: # 12

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 12
 Met Leu Pro Leu Glu Cys Gln Tyr Leu
 1 5

Information for SEQ ID No: # 13

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed peptide having an ability to activate HLA-A2 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 13

Thr Leu Leu Arg Lys Glu Arg Gly Val
1 5

Information for SEQ ID No: # 14

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed peptide having an ability to activate HLA-A2 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 14

Arg Ile Ile Tyr Asp Arg Lys Phe Leu
1 5

Information for SEQ ID No: # 15

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed peptide having an ability to activate HLA-A2 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 15

Ile Ile Tyr Asp Arg Lys Phe Leu Met
1 5

Information for SEQ ID No: # 16

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed peptide having an ability to activate HLA-A2 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 16

Gln Ile Leu Lys Gly Leu Leu Phe Leu
1 5

Information for SEQ ID No: # 17

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 17
Gly Leu Leu Phe Leu His Thr Arg Thr
1 5

Information for SEQ ID No: # 18

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 18
Asp Leu Leu Ser His Ala Phe Phe Ala
1 5

Information for SEQ ID No: # 19

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 19
Gln Gln Leu Cys Val Tyr Trp Thr Val
1 5

Information for SEQ ID No: # 20

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 20
Ser Leu Leu Tyr Leu Asn Gln Ser Val
1 5

Information for SEQ ID No: # 21

SEQUENCE CHARACTERISTICS

Length: 9

Type: PRT

ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
5

peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 21
Lys Val His Pro Val Ile Trp Ser Leu
1 5

Information for SEQ ID No: # 22
SEQUENCE CHARACTERISTICS
Length: 9
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 22
Asp Met Trp Thr Val Ile Ala Pro Val
1 5

Information for SEQ ID No: # 23
SEQUENCE CHARACTERISTICS
Length: 9
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 23
Gln Leu Gly Gln Gly Asn Leu Lys Val
1 5

Information for SEQ ID No: # 24
SEQUENCE CHARACTERISTICS
Length: 9
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 24
Leu Leu Leu Lys Tyr Thr Glu Lys Leu
1 5

Information for SEQ ID No: # 25
SEQUENCE CHARACTERISTICS
Length: 9
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 25
Thr Met Leu Pro His His Ala Gly Leu

1

5

Information for SEQ ID No: # 26
 SEQUENCE CHARACTERISTICS
 Length: 9
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 26
 Leu Leu Arg Arg Ala Asp Phe His Val
 1 5

Information for SEQ ID No: # 27
 SEQUENCE CHARACTERISTICS
 Length: 9
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 27
 Glu Leu Leu Asn Arg Tyr Leu Tyr Leu
 1 5

Information for SEQ ID No: # 28
 SEQUENCE CHARACTERISTICS
 Length: 9
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 28
 Leu Leu Met Leu Gln Asn Ala Leu Thr
 1 5

Information for SEQ ID No: # 29
 SEQUENCE CHARACTERISTICS
 Length: 9
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 29
 Tyr Gln Leu Pro Asp Trp Arg Leu Val
 1 5

Information for SEQ ID No: # 30
 SEQUENCE CHARACTERISTICS

Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 30
 Leu Met Leu Gln Asn Ala Leu Thr Thr Met
 1 5 10

Information for SEQ ID No: # 31

SEQUENCE CHARACTERISTICS

Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 31
 Leu Leu Met Leu Gln Asn Ala Leu Thr Thr
 1 5 10

Information for SEQ ID No: # 32

SEQUENCE CHARACTERISTICS

Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 32
 Thr Gln Leu Ala Thr Tyr Ser Phe Glu Val
 1 5 10

Information for SEQ ID No: # 33

SEQUENCE CHARACTERISTICS

Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 33
 Leu Glu Trp Tyr Asp Asp Phe Pro His Val
 1 5 10

Information for SEQ ID No: # 34

SEQUENCE CHARACTERISTICS

Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 34
Phe Ser Gly Asp Val Met Ile His Pro Val
1 5 10

Information for SEQ ID No: # 35
SEQUENCE CHARACTERISTICS
Length: 9
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 35
Trp Ala Gln Glu Asp Pro Asn Ala Val
1 5

Information for SEQ ID No: # 36
SEQUENCE CHARACTERISTICS
Length: 10
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 36
Ala Val Leu Gly Arg His Lys Met His Val
1 5 10

Information for SEQ ID No: # 37
SEQUENCE CHARACTERISTICS
Length: 10
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 37
Arg Leu Trp Glu Val Ala Thr Ala Arg Cys
1 5 10

Information for SEQ ID No: # 38
SEQUENCE CHARACTERISTICS
Length: 9
Type: PRT
ORIGINAL SOURCE: Artificial Sequence

Feature
Other Information: Description of Artificial Sequence:Designed
peptide having an ability to activate HLA-A2
restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 38

Val Ala Trp Asn Pro Ser Pro Ala Val
 1 5

Information for SEQ ID No: # 39
 SEQUENCE CHARACTERISTICS
 Length: 9
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 39
 Asp Leu Leu Gln Asn Pro Leu Leu Val
 1 5

Information for SEQ ID No: # 40
 SEQUENCE CHARACTERISTICS
 Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 40
 Leu Leu Gln Asn Pro Leu Leu Val Pro Val
 1 5 10

Information for SEQ ID No: # 41
 SEQUENCE CHARACTERISTICS
 Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 41
 Val Ile Phe His Pro Thr Gln Pro Trp Val
 1 5 10

Information for SEQ ID No: # 42
 SEQUENCE CHARACTERISTICS
 Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature
 Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 42
 Asn Leu Val Arg Asp Asp Gly Ser Ala Val
 1 5 10

Information for SEQ ID No: # 43

SEQUENCE CHARACTERISTICS

Length: 9
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 43

Arg Leu Phe Ala Phe Val Arg Phe Thr
 1 5

Information for SEQ ID No: # 44

SEQUENCE CHARACTERISTICS

Length: 10
 Type: PRT
 ORIGINAL SOURCE: Artificial Sequence

Feature

Other Information: Description of Artificial Sequence:Designed
 peptide having an ability to activate HLA-A2
 restricted Cytotoxic T lymphocytes

SEQUENCE DESCRIPTION: SEQ ID NO: 44

Val Val Gln Asn Phe Ala Lys Glu Phe Val
 1 5 10

Information for SEQ ID No: # 45

SEQUENCE CHARACTERISTICS

Length: 270
 Type: PRT
 ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 45

Met Ala Gly Ala Glu Asp Trp Pro Gly Gln Gln Leu Glu Leu Asp Glu
 1 5 10 15

Asp Glu Ala Ser Cys Cys Arg Trp Gly Ala Gln His Ala Gly Ala Arg
 20 25 30

Glu Leu Ala Ala Leu Tyr Ser Pro Gly Lys Arg Leu Gln Glu Trp Cys
 35 40 45

Ser Val Ile Leu Cys Phe Ser Leu Ile Ala His Asn Leu Val His Leu
 50 55 60

Leu Leu Leu Ala Arg Trp Glu Asp Thr Pro Leu Val Ile Leu Gly Val
 65 70 75 80

Val Ala Gly Ala Leu Ile Ala Asp Phe Leu Ser Gly Leu Val His Trp
 85 90 95

Gly Ala Asp Thr Trp Gly Ser Val Glu Leu Pro Ile Val Gly Lys Ala
 100 105 110

Phe Ile Arg Pro Phe Arg Glu His His Ile Asp Pro Thr Ala Ile Thr
 115 120 125

Arg His Asp Phe Ile Glu Thr Asn Gly Asp Asn Cys Leu Val Thr Leu
 130 135 140

Leu Pro Leu Leu Asn Met Ala Tyr Lys Phe Arg Thr His Ser Pro Glu
 145 150 155 160

Ala Leu Glu Gln Leu Tyr Pro Trp Glu Cys Phe Val Phe Cys Leu Ile
 11

				165					170					175			
Ile	Phe	Gly	Thr	Phe	Thr	Asn	Gln	Ile	His	Lys	Trp	Ser	His	Thr	Tyr		
			180					185					190				
Phe	Gly	Leu	Pro	Arg	Trp	Val	Thr	Leu	Leu	Gln	Asp	Trp	His	Val	Ile		
		195					200					205					
Leu	Pro	Arg	Lys	His	His	Arg	Ile	His	His	Val	Ser	Pro	His	Glu	Thr		
		210				215					220						
Tyr	Phe	Cys	Ile	Thr	Thr	Gly	Trp	Leu	Asn	Tyr	Pro	Leu	Glu	Lys	Ile		
225					230					235					240		
Gly	Phe	Trp	Arg	Arg	Leu	Glu	Asp	Leu	Ile	Gln	Gly	Leu	Thr	Gly	Glu		
				245					250					255			
Lys	Pro	Arg	Ala	Asp	Asp	Met	Lys	Trp	Ala	Gln	Lys	Ile	Lys				
			260					265					270				

Information for SEQ ID No: # 46

SEQUENCE CHARACTERISTICS

Length: 589

Type: PRT

ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 46

Met	Ser	Arg	Arg	Leu	Leu	Pro	Arg	Ala	Glu	Lys	Arg	Arg	Arg	Arg	Leu		
1				5					10					15			
Glu	Gln	Arg	Gln	Gln	Pro	Asp	Glu	Gln	Arg	Arg	Arg	Ser	Gly	Ala	Met		
			20					25					30				
Val	Lys	Met	Ala	Ala	Ala	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Arg	Tyr	Tyr		
		35				40						45					
Gly	Gly	Gly	Ser	Glu	Gly	Gly	Arg	Ala	Pro	Lys	Arg	Leu	Lys	Thr	Asp		
	50				55					60							
Asn	Ala	Gly	Asp	Gln	His	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Gly	Ala		
65				70				75							80		
Gly	Ala	Ala	Gly	Gly	Gly	Gly	Gly	Gly	Glu	Asn	Tyr	Asp	Asp	Pro	His		
			85						90					95			
Lys	Thr	Pro	Ala	Ser	Pro	Val	Val	His	Ile	Arg	Gly	Leu	Ile	Asp	Gly		
			100					105					110				
Val	Val	Glu	Ala	Asp	Leu	Val	Glu	Ala	Leu	Gln	Glu	Phe	Gly	Pro	Ile		
		115					120					125					
Ser	Tyr	Val	Val	Val	Met	Pro	Lys	Lys	Arg	Gln	Ala	Leu	Val	Glu	Phe		
	130				135						140						
Glu	Asp	Val	Leu	Gly	Ala	Cys	Asn	Ala	Val	Asn	Tyr	Ala	Ala	Asp	Asn		
145				150						155					160		
Gln	Ile	Tyr	Ile	Ala	Gly	His	Pro	Ala	Phe	Val	Asn	Tyr	Ser	Thr	Ser		
			165					170						175			
Gln	Lys	Ile	Ser	Arg	Pro	Gly	Asp	Ser	Asp	Asp	Ser	Arg	Ser	Val	Asn		
		180						185						190			
Ser	Val	Leu	Leu	Phe	Thr	Ile	Leu	Asn	Pro	Ile	Tyr	Ser	Ile	Thr	Thr		
		195					200					205					
Asp	Val	Leu	Tyr	Thr	Ile	Cys	Asn	Pro	Cys	Gly	Pro	Val	Gln	Arg	Ile		
	210					215					220						

Val 225	Ile	Phe	Arg	Lys	Asn 230	Gly	Val	Gln	Ala	Met 235	Val	Glu	Phe	Asp	Ser 240
Val	Gln	Ser	Ala	Gln 245	Arg	Ala	Lys	Ala	Ser 250	Leu	Asn	Gly	Ala	Asp 255	Ile
Tyr	Ser	Gly	Cys 260	Cys	Thr	Leu	Lys	Ile 265	Glu	Tyr	Ala	Lys	Pro 270	Thr	Arg
Leu	Asn	Val 275	Phe	Lys	Asn	Asp	Gln 280	Asp	Thr	Trp	Asp	Tyr 285	Thr	Asn	Pro
Asn	Leu 290	Ser	Gly	Gln	Gly	Asp 295	Pro	Gly	Ser	Asn	Pro 300	Asn	Lys	Arg	Gln
Arg 305	Gln	Pro	Pro	Leu	Leu 310	Gly	Asp	His	Pro	Ala 315	Glu	Tyr	Gly	Gly	Pro 320
His	Gly	Gly	Tyr	His 325	Ser	His	Tyr	His	Asp 330	Glu	Gly	Tyr	Gly	Pro 335	Pro
Pro	Pro	His	Tyr 340	Glu	Gly	Arg	Arg	Met 345	Gly	Pro	Pro	Val	Gly 350	Gly	His
Arg	Arg	Gly 355	Pro	Ser	Arg	Tyr	Gly 360	Pro	Gln	Tyr	Gly	His 365	Pro	Pro	Pro
Pro	Pro 370	Pro	Pro	Pro	Glu	Tyr 375	Gly	Pro	His	Ala	Asp 380	Ser	Pro	Val	Leu
Met 385	Val	Tyr	Gly	Leu	Asp 390	Gln	Ser	Lys	Met	Asn 395	Gly	Asp	Arg	Val	Phe 400
Asn	Val	Phe	Cys	Leu 405	Tyr	Gly	Asn	Val	Glu 410	Lys	Val	Lys	Phe	Met 415	Lys
Ser	Lys	Pro	Gly 420	Ala	Ala	Met	Val	Glu 425	Met	Ala	Asp	Gly	Tyr 430	Ala	Val
Asp	Arg	Ala 435	Ile	Thr	His	Leu	Asn 440	Asn	Asn	Phe	Met	Phe 445	Gly	Gln	Lys
Leu	Asn 450	Val	Cys	Val	Ser	Lys 455	Gln	Pro	Ala	Ile	Met 460	Pro	Gly	Gln	Ser
Tyr 465	Gly	Leu	Glu	Asp	Gly 470	Ser	Cys	Ser	Tyr	Lys 475	Asp	Phe	Ser	Glu	Ser 480
Arg	Asn	Asn	Arg	Phe 485	Ser	Thr	Pro	Glu	Gln 490	Ala	Ala	Lys	Asn	Arg 495	Ile
Gln	His	Pro	Ser 500	Asn	Val	Leu	His	Phe 505	Phe	Asn	Ala	Pro	Leu 510	Glu	Val
Thr	Glu	Glu 515	Asn	Phe	Phe	Glu	Ile 520	Cys	Asp	Glu	Leu	Gly 525	Val	Lys	Arg
Pro	Ser 530	Ser	Val	Lys	Val	Phe 535	Ser	Gly	Lys	Ser	Glu 540	Arg	Ser	Ser	Ser
Gly 545	Leu	Leu	Glu	Trp	Glu 550	Ser	Lys	Ser	Asp	Ala 555	Leu	Glu	Thr	Leu	Gly 560
Phe	Leu	Asn	His	Tyr 565	Gln	Met	Lys	Asn	Pro 570	Asn	Gly	Pro	Tyr	Pro 575	Tyr
Thr	Leu	Lys	Leu 580	Cys	Phe	Ser	Thr	Ala 585	Gln	His	Ala	Ser			

Information for SEQ ID No: # 47

SEQUENCE CHARACTERISTICS

Length: 549

Type: PRT

ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 47

```

Met Ala Ser Met Arg Glu Ser Asp Thr Gly Leu Trp Leu His Asn Lys
 1           5           10           15
Leu Gly Ala Thr Asp Glu Leu Trp Ala Pro Pro Ser Ile Ala Ser Leu
           20           25           30
Leu Thr Ala Ala Ile Ile Asp Asn Ile Arg Leu Cys Phe His Gly Leu
           35           40           45
Ser Ser Ala Ser Leu Leu Thr Ala Ala Val Ile Asp Asn Ile Arg Leu
           50           55           60
Cys Phe His Gly Leu Ser Ser Ala Val Lys Leu Lys Leu Leu Leu Gly
 65           70           75           80
Thr Leu His Leu Pro Arg Arg Thr Val Asp Glu Met Lys Gly Ala Leu
           85           90           95
Met Glu Ile Ile Gln Leu Ala Ser Leu Asp Ser Asp Pro Trp Val Leu
           100          105          110
Met Val Ala Asp Ile Leu Lys Ser Phe Pro Asp Thr Gly Ser Leu Asn
           115          120          125
Leu Glu Leu Glu Glu Gln Asn Pro Asn Val Gln Asp Ile Leu Gly Glu
           130          135          140
Leu Arg Glu Lys Val Gly Glu Cys Glu Ala Ser Ala Met Leu Pro Leu
           145          150          155          160
Glu Cys Gln Tyr Leu Asn Lys Asn Ala Leu Thr Thr Leu Ala Gly Pro
           165          170          175
Leu Thr Pro Pro Val Lys His Phe Gln Leu Lys Arg Lys Pro Lys Ser
           180          185          190
Ala Thr Leu Arg Ala Glu Leu Leu Gln Lys Ser Thr Glu Thr Ala Gln
           195          200          205
Gln Leu Lys Arg Ser Ala Gly Val Pro Phe His Ala Lys Gly Arg Gly
           210          215          220
Leu Leu Arg Lys Met Asp Thr Thr Thr Pro Leu Lys Gly Ile Pro Lys
           225          230          235          240
Gln Ala Pro Phe Arg Ser Pro Thr Ala Pro Ser Val Phe Ser Pro Thr
           245          250          255
Gly Asn Arg Thr Pro Ile Pro Pro Ser Arg Thr Leu Leu Arg Lys Glu
           260          265          270
Arg Gly Val Lys Leu Leu Asp Ile Ser Glu Leu Asp Met Val Gly Ala
           275          280          285
Gly Arg Glu Ala Lys Arg Arg Arg Lys Thr Leu Asp Ala Glu Val Val
           290          295          300
Glu Lys Pro Ala Lys Glu Glu Thr Val Val Glu Asn Ala Thr Pro Asp
           305          310          315          320

```

SEQUENCE CHARACTERISTICS

Type: PRT

SEQUENCE DESCRIPTION: SEQ ID NO: 48

Val Thr Ser Pro Ser Ser Asp Glu Pro Pro Met Glu Ala Ser Gln Ser
15

85 90 95

His Leu Arg Asn Ser Pro Glu Asp Lys Arg Ala Gly Gly Glu Glu Ser
100 105 110

Gln Phe Glu Met Asp Ile
115

Information for SEQ ID No: # 49
SEQUENCE CHARACTERISTICS
Length: 779
Type: PRT
ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 49																
Met 1	Glu	Pro	Gly	Arg 5	Gly	Ala	Gly	Pro	Ala 10	Gly	Met	Ala	Glu	Pro 15	Arg	
Ala	Lys	Ala	Ala 20	Arg	Pro	Gly	Pro	Gln 25	Arg	Phe	Leu	Arg	Arg 30	Ser	Val	
Val	Glu	Ser 35	Asp	Gln	Glu	Glu	Pro 40	Pro	Gly	Leu	Glu	Ala 45	Ala	Glu	Ala	
Pro	Gly 50	Pro	Gln	Pro	Pro	Gln 55	Pro	Leu	Gln	Arg	Arg 60	Val	Leu	Leu	Leu	
Cys 65	Lys	Thr	Arg	Arg	Leu 70	Ile	Ala	Glu	Arg	Ala 75	Arg	Gly	Arg	Pro	Ala 80	
Ala	Pro	Ala	Pro	Ala 85	Ala	Leu	Val	Ala	Gln 90	Pro	Gly	Ala	Pro	Gly 95	Ala	
Pro	Ala	Asp	Ala 100	Gly	Pro	Glu	Pro	Val 105	Gly	Thr	Gln	Glu	Pro 110	Gly	Pro	
Asp	Pro	Ile 115	Ala	Ala	Ala	Val	Glu 120	Thr	Ala	Pro	Ala	Pro 125	Asp	Gly	Gly	
Pro	Arg 130	Glu	Glu	Ala	Ala	Ala 135	Thr	Val	Arg	Lys	Glu 140	Asp	Glu	Gly	Ala	
Ala 145	Glu	Ala	Lys	Pro	Glu 150	Pro	Gly	Arg	Thr	Arg 155	Arg	Asp	Glu	Pro	Glu 160	
Glu	Glu	Glu	Asp	Asp 165	Glu	Asp	Asp	Leu	Lys 170	Ala	Val	Ala	Thr	Ser 175	Leu	
Asp	Gly	Arg	Phe 180	Leu	Lys	Phe	Asp	Ile 185	Glu	Leu	Gly	Arg	Gly 190	Ser	Phe	
Lys	Thr	Val 195	Tyr	Lys	Gly	Leu	Asp 200	Thr	Glu	Thr	Trp	Val 205	Glu	Val	Ala	
Trp	Cys 210	Glu	Leu	Gln	Asp	Arg 215	Lys	Leu	Thr	Lys	Leu 220	Glu	Arg	Gln	Arg	
Phe 225	Lys	Glu	Glu	Ala	Glu 230	Met	Leu	Lys	Gly	Leu 235	Gln	His	Pro	Asn	Ile 240	
Val	Arg	Phe	Tyr	Asp 245	Phe	Trp	Glu	Ser	Ser 250	Ala	Lys	Gly	Lys	Arg 255	Cys	
Ile	Val	Leu	Val 260	Thr	Glu	Leu	Met	Thr 265	Ser	Gly	Thr	Leu	Lys 270	Thr	Tyr	
Leu	Lys	Arg 275	Phe	Lys	Val	Met	Lys 280	Pro	Lys	Val	Leu	Arg 285	Ser	Trp	Cys	

Arg	Gln	Ile	Leu	Lys	Gly	Leu	Leu	Phe	Leu	His	Thr	Arg	Thr	Pro	Pro
	290					295					300				
Ile	Ile	His	Arg	Asp	Leu	Lys	Cys	Asp	Asn	Ile	Phe	Ile	Thr	Gly	Pro
305					310					315					320
Thr	Gly	Ser	Val	Lys	Ile	Gly	Asp	Leu	Gly	Leu	Ala	Thr	Leu	Lys	Arg
				325					330					335	
Ala	Ser	Phe	Ala	Lys	Ser	Val	Ile	Gly	Thr	Pro	Glu	Phe	Met	Ala	Pro
			340					345					350		
Glu	Met	Tyr	Glu	Glu	His	Tyr	Asp	Glu	Ser	Val	Asp	Val	Tyr	Ala	Phe
		355					360					365			
Gly	Met	Cys	Met	Leu	Glu	Met	Ala	Thr	Ser	Glu	Tyr	Pro	Tyr	Ser	Glu
	370					375					380				
Cys	Gln	Asn	Ala	Ala	Gln	Ile	Tyr	Arg	Lys	Val	Thr	Cys	Gly	Ile	Lys
385					390					395					400
Pro	Ala	Ser	Phe	Glu	Lys	Val	His	Asp	Pro	Glu	Ile	Lys	Glu	Ile	Ile
				405					410					415	
Gly	Glu	Cys	Ile	Cys	Lys	Asn	Lys	Glu	Glu	Arg	Tyr	Glu	Ile	Lys	Asp
			420					425					430		
Leu	Leu	Ser	His	Ala	Phe	Phe	Ala	Glu	Asp	Thr	Gly	Val	Arg	Val	Glu
		435					440					445			
Leu	Ala	Glu	Glu	Asp	His	Gly	Arg	Lys	Ser	Thr	Ile	Ala	Leu	Arg	Leu
	450					455					460				
Trp	Val	Glu	Asp	Pro	Lys	Lys	Leu	Lys	Gly	Lys	Pro	Lys	Asp	Asn	Gly
465					470					475					480
Ala	Ile	Glu	Phe	Thr	Phe	Asp	Leu	Glu	Lys	Glu	Thr	Pro	Asp	Glu	Val
				485					490					495	
Ala	Gln	Glu	Met	Ile	Glu	Ser	Gly	Phe	Phe	His	Glu	Ser	Asp	Val	Lys
			500					505					510		
Ile	Val	Ala	Lys	Ser	Ile	Arg	Asp	Arg	Val	Ala	Leu	Ile	Gln	Trp	Arg
		515					520					525			
Arg	Glu	Arg	Ile	Trp	Pro	Ala	Leu	Gln	Pro	Lys	Glu	Gln	Gln	Asp	Val
	530					535					540				
Gly	Ser	Pro	Asp	Lys	Ala	Arg	Gly	Pro	Pro	Val	Pro	Leu	Gln	Val	Gln
545					550					555					560
Val	Thr	Tyr	His	Ala	Gln	Ala	Gly	Gln	Pro	Gly	Pro	Pro	Glu	Pro	Glu
				565					570					575	
Glu	Pro	Glu	Ala	Asp	Gln	His	Leu	Leu	Pro	Pro	Thr	Leu	Pro	Thr	Ser
			580					585					590		
Ala	Thr	Ser	Leu	Ala	Ser	Asp	Ser	Thr	Phe	Asp	Ser	Gly	Gln	Gly	Ser
		595					600					605			
Thr	Val	Tyr	Ser	Asp	Ser	Gln	Ser	Ser	Gln	Gln	Ser	Val	Met	Leu	Gly
	610					615					620				
Ser	Leu	Ala	Asp	Ala	Ala	Pro	Ser	Pro	Ala	Gln	Cys	Val	Cys	Ser	Pro
625					630					635					640
Pro	Val	Ser	Glu	Gly	Pro	Val	Leu	Pro	Gln	Ser	Leu	Pro	Ser	Leu	Gly
				645					650					655	

Ala Tyr Gln Gln Pro Thr Ala Ala Pro Pro Pro Leu Ala Gln Pro Thr
660 665 670
Pro Leu Pro Gln Val Leu Ala Pro Gln Pro Val Val Pro Leu Gln Pro
675 680 685
Val Pro Pro His Leu Pro Pro Tyr Leu Ala Pro Ala Ser Gln Val Gly
690 695 700
Ala Pro Ala Gln Leu Lys Pro Leu Gln Met Pro Gln Ala Pro Leu Gln
705 710 715 720
Pro Leu Ala Gln Val Pro Pro Gln Met Pro Pro Ile Pro Val Val Pro
725 730 735
Pro Ile Thr Pro Leu Ala Gly Ile Asp Gly Leu Pro Pro Ala Leu Pro
740 745 750
Asp Leu Pro Thr Ala Thr Val Pro Pro Val Pro Pro Pro Gln Tyr Phe
755 760 765
Ser Pro Ala Val Ile Leu Pro Ser Arg Thr Arg
770 775

Information for SEQ ID No: # 50

SEQUENCE CHARACTERISTICS

Length: 1087

Type: PRT

ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 50

Met Asp Leu Tyr Ser Thr Pro Ala Ala Ala Leu Asp Arg Phe Val Ala
1 5 10 15
Arg Lys Leu Gln Pro Arg Lys Glu Phe Val Glu Lys Ala Arg Arg Ala
20 25 30
Leu Gly Ala Leu Ala Ala Ala Leu Arg Glu Arg Gly Gly Arg Leu Gly
35 40 45
Ala Ala Ala Pro Arg Val Leu Lys Thr Val Lys Gly Gly Ser Ser Gly
50 55 60
Arg Gly Thr Ala Leu Lys Gly Gly Cys Asp Ser Glu Leu Val Ile Phe
65 70 75 80
Leu Asp Cys Phe Lys Ser Tyr Val Asp Gln Arg Ala Arg Arg Ala Glu
85 90 95
Ile Leu Ser Glu Met Arg Ala Ser Leu Glu Ser Trp Trp Gln Asn Pro
100 105 110
Val Pro Gly Leu Arg Leu Thr Phe Pro Glu Gln Ser Val Pro Gly Ala
115 120 125
Leu Gln Phe Arg Leu Thr Ser Val Asp Leu Glu Asp Trp Met Asp Val
130 135 140
Ser Leu Val Pro Ala Phe Asn Val Leu Gly Gln Ala Gly Ser Gly Val
145 150 155 160
Lys Pro Lys Pro Gln Val Tyr Ser Thr Leu Leu Asn Ser Gly Cys Gln
165 170 175
Gly Gly Glu His Ala Ala Cys Phe Thr Glu Leu Arg Arg Asn Phe Val
180 185 190

Asn	Ile	Arg	Pro	Ala	Lys	Leu	Lys	Asn	Leu	Ile	Leu	Leu	Val	Lys	His
		195					200					205			
Trp	Tyr	His	Gln	Val	Cys	Leu	Gln	Gly	Leu	Trp	Lys	Glu	Thr	Leu	Pro
	210					215					220				
Pro	Val	Tyr	Ala	Leu	Glu	Leu	Leu	Thr	Ile	Phe	Ala	Trp	Glu	Gln	Gly
225					230					235					240
Cys	Lys	Lys	Asp	Ala	Phe	Ser	Leu	Ala	Glu	Gly	Leu	Arg	Thr	Val	Leu
				245					250					255	
Gly	Leu	Ile	Gln	Gln	His	Gln	His	Leu	Cys	Val	Phe	Trp	Thr	Val	Asn
			260					265					270		
Tyr	Gly	Phe	Glu	Asp	Pro	Ala	Val	Gly	Gln	Phe	Leu	Gln	Arg	Gln	Leu
		275					280					285			
Lys	Arg	Pro	Arg	Pro	Val	Ile	Leu	Asp	Pro	Ala	Asp	Pro	Thr	Trp	Asp
	290					295					300				
Leu	Gly	Asn	Gly	Ala	Ala	Trp	His	Trp	Asp	Leu	Leu	Ala	Gln	Glu	Ala
305					310					315					320
Ala	Ser	Cys	Tyr	Asp	His	Pro	Cys	Phe	Leu	Arg	Gly	Met	Gly	Asp	Pro
				325					330					335	
Val	Gln	Ser	Trp	Lys	Gly	Pro	Gly	Leu	Pro	Arg	Ala	Gly	Cys	Ser	Gly
			340					345					350		
Leu	Gly	His	Pro	Ile	Gln	Leu	Asp	Pro	Asn	Gln	Lys	Thr	Pro	Glu	Asn
		355					360					365			
Ser	Lys	Ser	Leu	Asn	Ala	Val	Tyr	Pro	Arg	Ala	Gly	Ser	Lys	Pro	Pro
	370					375					380				
Ser	Cys	Pro	Ala	Pro	Gly	Pro	Thr	Gly	Ala	Ala	Ser	Ile	Val	Pro	Ser
385					390				395						400
Val	Pro	Gly	Met	Ala	Leu	Asp	Leu	Ser	Gln	Ile	Pro	Thr	Lys	Glu	Leu
				405					410					415	
Asp	Arg	Phe	Ile	Gln	Asp	His	Leu	Lys	Pro	Ser	Pro	Gln	Phe	Gln	Glu
			420					425					430		
Gln	Val	Lys	Lys	Ala	Ile	Asp	Ile	Ile	Leu	Arg	Cys	Leu	His	Glu	Asn
		435					440					445			
Cys	Val	His	Lys	Ala	Ser	Arg	Val	Ser	Lys	Gly	Gly	Ser	Phe	Gly	Arg
	450					455					460				
Gly	Thr	Asp	Leu	Arg	Asp	Gly	Cys	Asp	Val	Glu	Leu	Ile	Ile	Phe	Leu
465					470					475					480
Asn	Cys	Phe	Thr	Asp	Tyr	Lys	Asp	Gln	Gly	Pro	Arg	Arg	Ala	Glu	Ile
				485					490					495	
Leu	Asp	Glu	Met	Arg	Ala	His	Val	Glu	Ser	Trp	Trp	Gln	Asp	Gln	Val
			500					505					510		
Pro	Ser	Leu	Ser	Leu	Gln	Phe	Pro	Glu	Gln	Asn	Val	Pro	Glu	Ala	Leu
		515					520					525			
Gln	Phe	Gln	Leu	Val	Ser	Thr	Ala	Leu	Lys	Ser	Trp	Thr	Asp	Val	Ser
	530					535					540				
Leu	Leu	Pro	Ala	Phe	Asp	Ala	Val	Gly	Gln	Leu	Ser	Ser	Gly	Thr	Lys
545					550				555						560

Pro	Asn	Pro	Gln	Val 565	Tyr	Ser	Arg	Leu	Leu 570	Thr	Ser	Gly	Cys	Gln 575	Glu	
Gly	Glu	His	Lys 580	Ala	Cys	Phe	Ala	Glu 585	Leu	Arg	Arg	Asn	Phe 590	Met	Asn	
Ile	Arg	Pro 595	Val	Lys	Leu	Lys	Asn 600	Leu	Ile	Leu	Leu	Val 605	Lys	His	Trp	
Tyr	Arg 610	Gln	Val	Ala	Ala	Gln 615	Asn	Lys	Gly	Lys	Gly 620	Pro	Ala	Pro	Ala	
Ser 625	Leu	Pro	Pro	Ala	Tyr 630	Ala	Leu	Glu	Leu	Leu 635	Thr	Ile	Phe	Ala	Trp 640	
Glu	Gln	Gly	Cys	Arg 645	Gln	Asp	Cys	Phe	Asn 650	Met	Ala	Gln	Gly	Phe 655	Arg	
Thr	Val	Leu	Gly 660	Leu	Val	Gln	Gln	His 665	Gln	Gln	Leu	Cys	Val 670	Tyr	Trp	
Thr	Val	Asn 675	Tyr	Ser	Thr	Glu	Asp 680	Pro	Ala	Met	Arg	Met 685	His	Leu	Leu	
Gly	Gln 690	Leu	Arg	Lys	Pro	Arg 695	Pro	Leu	Val	Leu	Asp 700	Pro	Ala	Asp	Pro	
Thr 705	Trp	Asn	Val	Gly	His 710	Gly	Ser	Trp	Glu	Leu 715	Leu	Ala	Gln	Glu	Ala 720	
Ala	Ala	Leu	Gly	Met 725	Gln	Ala	Cys	Phe	Leu 730	Ser	Arg	Asp	Gly	Thr 735	Ser	
Val	Gln	Pro	Trp 740	Asp	Val	Met	Pro	Ala 745	Leu	Leu	Tyr	Gln	Thr 750	Pro	Ala	
Gly	Asp	Leu 755	Asp	Lys	Phe	Ile	Ser 760	Glu	Phe	Leu	Gln	Pro 765	Asn	Arg	Gln	
Phe 770	Leu	Ala	Gln	Val	Asn	Lys 775	Ala	Val	Asp	Thr	Ile 780	Cys	Ser	Phe	Leu	
Lys 785	Glu	Asn	Cys	Phe	Arg 790	Asn	Ser	Pro	Ile	Lys 795	Val	Ile	Lys	Val	Val 800	
Lys	Gly	Gly	Ser	Ser 805	Ala	Lys	Gly	Thr	Ala 810	Leu	Arg	Gly	Arg	Ser 815	Asp	
Ala	Asp	Leu	Val 820	Val	Phe	Leu	Ser	Cys 825	Phe	Ser	Gln	Phe	Thr 830	Glu	Gln	
Gly	Asn	Lys 835	Arg	Ala	Glu	Ile	Ile 840	Ser	Glu	Ile	Arg	Ala 845	Gln	Leu	Glu	
Ala	Cys 850	Gln	Gln	Glu	Arg	Gln 855	Phe	Glu	Val	Lys	Phe 860	Glu	Val	Ser	Lys	
Trp 865	Glu	Asn	Pro	Arg	Val 870	Leu	Ser	Phe	Ser	Leu 875	Thr	Ser	Gln	Thr	Met 880	
Leu	Asp	Gln	Ser	Val 885	Asp	Phe	Asp	Val	Leu 890	Pro	Ala	Phe	Asp	Ala 895	Leu	
Gly	Gln	Leu	Val 900	Ser	Gly	Ser	Arg	Pro 905	Ser	Ser	Gln	Val	Tyr 910	Val	Asp	
Leu	Ile	His 915	Ser	Tyr	Ser	Asn	Ala 920	Gly	Glu	Tyr	Ser	Thr 925	Cys	Phe	Thr	

Glu Leu Gln Arg Asp Phe Ile Ile Ser Arg Pro Thr Lys Leu Lys Ser
 930 935 940
 Leu Ile Arg Leu Val Lys His Trp Tyr Gln Gln Cys Thr Lys Ile Ser
 945 950 955 960
 Lys Gly Arg Gly Ser Leu Pro Pro Gln His Gly Leu Glu Leu Leu Thr
 965 970 975
 Val Tyr Ala Trp Glu Gln Gly Arg Lys Asp Ser Gln Phe Asn Met Ala
 980 985 990
 Glu Gly Phe Arg Thr Val Leu Glu Leu Val Thr Gln Tyr Arg Gln Leu
 995 1000 1005
 Cys Ile Tyr Trp Thr Ile Asn Tyr Asn Ala Lys Asp Lys Thr Val Gly
 1010 1015 1020
 Asp Phe Leu Lys Gln Gln Leu Gln Lys Pro Arg Pro Ile Ile Leu Asp
 1025 1030 1035 1040
 Pro Ala Asp Pro Thr Gly Asn Leu Gly His Asn Ala Arg Trp Asp Leu
 1045 1050 1055
 Leu Ala Lys Glu Ala Ala Ala Cys Thr Ser Ala Leu Cys Cys Met Gly
 1060 1065 1070
 Arg Asn Gly Ile Pro Ile Gln Pro Trp Pro Val Lys Ala Ala Val
 1075 1080 1085

Information for SEQ ID No: # 51

SEQUENCE CHARACTERISTICS

Length: 216

Type: PRT

ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 51

Met Lys Ser Ile Ser Leu Leu Arg Tyr Gln Glu Glu Ser Lys Thr Leu
 1 5 10 15
 Ser Leu Val Ser Arg Asp Ala Lys Pro Leu Glu Val Tyr Ser Val Asp
 20 25 30
 Phe Met Val Asp Asn Ala Gln Leu Gly Phe Leu Val Ser Asp Arg Asp
 35 40 45
 Arg Asn Leu Met Val Tyr Met Tyr Leu Pro Glu Ala Lys Glu Ser Phe
 50 55 60
 Gly Gly Met Arg Leu Leu Arg Arg Ala Asp Phe His Val Gly Ala His
 65 70 75 80
 Val Asn Thr Phe Trp Arg Thr Pro Cys Arg Gly Ala Thr Glu Gly Leu
 85 90 95
 Ser Lys Lys Ser Val Val Trp Glu Asn Lys His Ile Thr Trp Phe Ala
 100 105 110
 Thr Leu Asp Gly Gly Ile Gly Leu Leu Leu Pro Met Gln Glu Lys Thr
 115 120 125
 Tyr Arg Arg Leu Leu Met Leu Gln Asn Ala Leu Thr Thr Met Leu Pro
 130 135 140
 His His Ala Gly Leu Asn Pro Arg Ala Phe Arg Met Leu His Val Asp
 145 150 155 160
 Arg Arg Thr Leu Gln Asn Ala Val Arg Asn Val Leu Asp Gly Glu Leu
 21

				165						170					175
Leu	Asn	Arg	Tyr	Leu	Tyr	Leu	Ser	Thr	Met	Glu	Arg	Ser	Glu	Leu	Ala
			180					185					190		
Lys	Lys	Ile	Gly	Thr	Thr	Pro	Asp	Ile	Ile	Leu	Asp	Asp	Leu	Leu	Glu
		195					200					205			
Thr	Asp	Arg	Val	Thr	Ala	His	Phe								
	210					215									

Information for SEQ ID No: # 52
 SEQUENCE CHARACTERISTICS
 Length: 634
 Type: PRT
 ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 52

Met	Ala	Ser	Ala	Arg	Ile	Gly	Asp	Glu	Tyr	Ala	Glu	Asp	Ser	Ser	Asp
1				5					10					15	
Glu	Glu	Asp	Ile	Arg	Asn	Thr	Val	Gly	Asn	Val	Pro	Leu	Glu	Trp	Tyr
			20					25					30		
Asp	Asp	Phe	Pro	His	Val	Gly	Tyr	Asp	Leu	Asp	Gly	Arg	Arg	Ile	Tyr
		35					40					45			
Lys	Pro	Leu	Arg	Thr	Arg	Asp	Glu	Leu	Asp	Gln	Phe	Leu	Asp	Lys	Met
	50					55					60				
Asp	Asp	Pro	Asp	Tyr	Trp	Arg	Thr	Val	Gln	Asp	Pro	Met	Thr	Gly	Arg
65					70					75					80
Asp	Leu	Arg	Leu	Thr	Asp	Glu	Gln	Val	Ala	Leu	Val	Arg	Arg	Leu	Gln
				85					90					95	
Ser	Gly	Gln	Phe	Gly	Asp	Val	Gly	Phe	Asn	Pro	Tyr	Glu	Pro	Ala	Val
			100					105					110		
Asp	Phe	Phe	Ser	Gly	Asp	Val	Met	Ile	His	Pro	Val	Thr	Asn	Arg	Pro
		115					120					125			
Ala	Asp	Lys	Arg	Ser	Phe	Ile	Pro	Ser	Leu	Val	Glu	Lys	Glu	Lys	Val
	130					135					140				
Ser	Arg	Met	Val	His	Ala	Ile	Lys	Met	Gly	Trp	Ile	Gln	Pro	Arg	Arg
145					150					155					160
Pro	Arg	Asp	Pro	Thr	Pro	Ser	Phe	Tyr	Asp	Leu	Trp	Ala	Gln	Glu	Asp
				165					170					175	
Pro	Asn	Ala	Val	Leu	Gly	Arg	His	Lys	Met	His	Val	Pro	Ala	Pro	Lys
			180					185					190		
Leu	Ala	Leu	Pro	Gly	His	Ala	Glu	Ser	Tyr	Asn	Pro	Pro	Pro	Glu	Tyr
		195					200					205			
Leu	Leu	Ser	Glu	Glu	Glu	Arg	Leu	Ala	Trp	Glu	Gln	Gln	Glu	Pro	Gly
	210					215					220				
Glu	Arg	Lys	Leu	Ser	Phe	Leu	Pro	Arg	Lys	Phe	Pro	Ser	Leu	Arg	Ala
225					230					235					240
Val	Pro	Ala	Tyr	Gly	Arg	Phe	Ile	Gln	Glu	Arg	Phe	Glu	Arg	Cys	Leu
				245					250					255	
Asp	Leu	Tyr	Leu	Cys	Pro	Arg	Gln	Arg	Lys	Met	Arg	Val	Asn	Val	Asp
			260					265					270		

Pro Glu Asp Leu Ile Pro Lys Leu Pro Arg Pro Arg Asp Leu Gln Pro
 275 280 285
 Phe Pro Thr Cys Gln Ala Leu Val Tyr Arg Gly His Ser Asp Leu Val
 290 295 300
 Arg Cys Leu Ser Val Ser Pro Gly Gly Gln Trp Leu Val Ser Gly Ser
 305 310 315 320
 Asp Asp Gly Ser Leu Arg Leu Trp Glu Val Ala Thr Ala Arg Cys Val
 325 330 335
 Arg Thr Val Pro Val Gly Gly Val Val Lys Ser Val Ala Trp Asn Pro
 340 345 350
 Ser Pro Ala Val Cys Leu Val Ala Ala Ala Val Glu Asp Ser Val Leu
 355 360 365
 Leu Leu Asn Pro Ala Leu Gly Asp Arg Leu Val Ala Gly Ser Thr Asp
 370 375 380
 Gln Leu Leu Ser Ala Phe Val Pro Pro Glu Glu Pro Pro Leu Gln Pro
 385 390 395 400
 Ala Arg Trp Leu Glu Ala Ser Glu Glu Glu Arg Gln Val Gly Leu Arg
 405 410 415
 Leu Arg Ile Cys His Gly Lys Pro Val Thr Gln Val Thr Trp His Gly
 420 425 430
 Arg Gly Asp Tyr Leu Ala Val Val Leu Ala Thr Gln Gly His Thr Gln
 435 440 445
 Val Leu Ile His Gln Leu Ser Arg Arg Arg Ser Gln Ser Pro Phe Arg
 450 455 460
 Arg Ser His Gly Gln Val Gln Arg Val Ala Phe His Pro Ala Arg Pro
 465 470 475 480
 Phe Leu Leu Val Ala Ser Gln Arg Ser Val Arg Leu Tyr His Leu Leu
 485 490 495
 Arg Gln Glu Leu Thr Lys Lys Leu Met Pro Asn Cys Lys Trp Val Ser
 500 505 510
 Ser Leu Ala Val His Pro Ala Gly Asp Asn Val Ile Cys Gly Ser Tyr
 515 520 525
 Asp Ser Lys Leu Val Trp Phe Asp Leu Asp Leu Ser Thr Lys Pro Tyr
 530 535 540
 Arg Met Leu Arg His His Lys Lys Ala Leu Arg Ala Val Ala Phe His
 545 550 555 560
 Pro Arg Tyr Pro Leu Phe Ala Ser Gly Ser Asp Asp Gly Ser Val Ile
 565 570 575
 Val Cys His Gly Met Val Tyr Asn Asp Leu Leu Gln Asn Pro Leu Leu
 580 585 590
 Val Pro Val Lys Val Leu Lys Gly His Val Leu Thr Arg Asp Leu Gly
 595 600 605
 Val Leu Asp Val Ile Phe His Pro Thr Gln Pro Trp Val Phe Ser Ser
 610 615 620
 Gly Ala Asp Gly Thr Val Arg Leu Phe Thr
 625 630

Information for SEQ ID No: # 53

SEQUENCE CHARACTERISTICS

Length: 142

Type: PRT

ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 53

```

Met Ala Thr Lys Ile Asp Lys Glu Ala Cys Arg Ala Ala Tyr Asn Leu
 1           5           10          15
Val Arg Asp Asp Gly Ser Ala Val Ile Trp Val Thr Phe Lys Tyr Asp
          20          25          30
Gly Ser Thr Ile Val Pro Gly Glu Gln Gly Ala Glu Tyr Gln His Phe
          35          40          45
Ile Gln Gln Cys Thr Asp Asp Val Arg Leu Phe Ala Phe Val Arg Phe
          50          55          60
Thr Thr Gly Asp Ala Met Ser Lys Arg Ser Lys Phe Ala Leu Ile Thr
          65          70          75          80
Trp Ile Gly Glu Asn Val Ser Gly Leu Gln Arg Ala Lys Thr Gly Thr
          85          90          95
Asp Lys Thr Leu Val Lys Glu Val Val Gln Asn Phe Ala Lys Glu Phe
          100         105         110
Val Ile Ser Asp Arg Lys Glu Leu Glu Glu Asp Phe Ile Lys Ser Glu
          115         120         125
Leu Lys Lys Ala Gly Gly Ala Asn Tyr Asp Ala Gln Thr Glu
          130         135         140

```

Information for SEQ ID No: # 54

SEQUENCE CHARACTERISTICS

Length: 1775

Type: DNA

ORIGINAL SOURCE: Homo sapiens

Feature

Name/Key: misc_feature

Location: (37)

Other Information: n is A or G or C or T

Feature

Name/Key: misc_feature

Location: (41)

Other Information: n is A or G or C or T

Feature

Name/Key: polyA_site

Location: (1775)

SEQUENCE DESCRIPTION: SEQ ID NO: 54

```

atctcgccgc gggtccgcgg ccctgccgcc gccgccnttt ngcagagcgc accgggcccga 60
tcgggcgagt ggccatggcg ggcgccgagg actggccggg ccagcagctg gagctggacg 120
aggacgaggc gtcttggttg cgctggggcg cgcagcacgc cggggcccgc gagctggctg 180
cgctctactc gccaggcaag cgcctccagg agtggtgctc tgtgatcctg tgcttcagcc 240
tcatcgccca caacctggtc catctcctgc tgctggcccc ctgggaggac acaccctcg 300
tcatactcgg tggtgttgca ggggctctca ttgctgactt cttgtctggc ctggtacact 360
ggggtgctga cacatggggc tctgtggagc tgcccattgt ggggaaggct ttcacccgac 420
ccttccggga gcaccacatt gacccgacag ctatcacacg gcacgacttc atcgagacca 480
acggggacaa ctgcctggtg acactgctgc cgctgctaaa catggcctac aagttccgca 540
cccacagccc tgaagccctg gagcagctat acccctggga gtgcttcgtc ttctgcctga 600

```

tcatcttcgg	caccttcacc	aaccagatcc	acaagtgggtc	gcacacgtac	tttgggctgc	660
cacgctgggt	caccctcctg	caggactggc	atgtcatcct	gccacgtaaa	caccatcgca	720
tccaccacgt	ctcacccccac	gagacctact	tctgcatcac	cacaggctgg	ctcaactacc	780
ctctggagaa	gataggcttc	tggcgacgcc	tggaggacct	catccagggc	ctgacgggcg	840
agaagcctcg	ggcagatgac	atgaaatggg	cccagaagat	caaataactt	ctccgagcct	900
gctacctggt	tgccaacctt	ccctagcccc	caaaccgaag	ccatctgcca	aattccagcc	960
tctttgagct	ggccccctcca	gatggagagg	acatctcctg	ggctggggccc	aggtacccca	1020
gcccacccct	catgacacag	aatacttgag	ccactgattt	ttcattttctt	tttttttttt	1080
tcctcgggccc	ctcctcagcc	acctgagttg	ctctatctgc	aagcctgact	ctgccagcct	1140
cccctggtag	agaggagggt	taccactcc	ctgcacgcct	gccgtccctg	ccccgctggg	1200
caagcccttc	agtgtggctg	gcgttggggc	cagtgaagtg	cctctttccc	tccttgtctg	1260
gccccagtgg	tctggggagc	ccccaggcac	acctaagcgt	cgtggagcat	tggtctgcca	1320
cagccctgca	tactgacccc	gggaggctgg	gcagggtggac	agccccagcc	accaccttca	1380
gcctagcctg	tcccccaagg	atggtgaagc	tcagcagggg	tctgagggta	gccggccaga	1440
agaggctgga	acctcctgct	caagtctaga	cccctacttc	tctgctgccc	ccaccctgcc	1500
agagctgatg	tttccaatac	caagatgtct	tcacagggca	cagcccctgc	agagcatctt	1560
ggtcattttg	aagaggacac	ggtatcccct	ctggccagag	tatgtcagag	aaggaagagt	1620
agggcttttt	tgttttgttt	tttttttaaag	gtgcttgctt	gtttaatgta	aataatagaa	1680
agccttaata	tcttttctgt	aacacggagt	aatattttta	tgatcatgtt	tggatgtaca	1740
taatataatt	ataacaaagc	agcaagagtc	tactt			1775

Information for SEQ ID No: # 55

SEQUENCE CHARACTERISTICS

Length: 2097

Type: DNA

ORIGINAL SOURCE: Homo sapiens

Feature

Name/Key: polyA_site

Location: (2097)

SEQUENCE DESCRIPTION: SEQ ID NO: 55

gccgccatgt	cgcgagggt	gctgccccgg	gcggagaagc	ggcgtcggcg	gctggagcag	60
aggcagcagc	cggacgagca	gcggaggcgg	tcgggagcga	tggtgaagat	ggcggcgggcg	120
ggcggcgggag	gcggcggtgg	ccgctactac	ggcggcgggca	gtgagggcg	ccggggcccct	180
aagcggctca	agactgacaa	cgccggcgac	cagcacggag	gcggcgggcg	tggcgggtgga	240
ggagccgggg	cggcggggcg	cggcggcggt	ggggagaact	acgatgacct	gcacaaaacc	300
cctgcctccc	cagttgtcca	catcaggggc	ctgattgacg	gtgtggtgga	agcagacctt	360
gtggaggcct	tgcaggagtt	tggacccatc	agctatgtgg	tggtaatgcc	taaaaagaga	420
caagcactgg	tggagtttga	agatgtgttg	ggggcttgca	acgcagtga	ctacgcagcc	480
gacaaccaaa	tatacattgc	tggtcaccca	gcttttgtca	actactctac	cagccagaag	540
atctcccggc	ctggggactc	ggatgactcc	cggagcgtga	acagtgtgct	tctctttacc	600
atcctgaacc	ccatttattc	gatcaccacg	gatgttcttt	acactatctg	taatccttgt	660
ggccctgtcc	agagaattgt	cattttccag	agaatggag	ttcaggcgat	ggtggaattt	720
gactcagttc	aaagtgccc	gcggggccaag	gcctctctca	atggggctga	tatctattct	780
ggctgttgca	ctctgaagat	cgaatacgca	aagcctacac	gcttgaatgt	gttcaagaat	840
gatcaggata	cttgggacta	cacaaacccc	aatctcagtg	gacaagggtga	ccctggcagc	900
aaccccaaca	aacgccagag	gcagccccct	ctcctgggag	atcaccccg	agaatatgga	960
gggccccacg	gtgggtacca	cagccattac	catgatgagg	gctacggggc	ccccccacct	1020
cactacgaag	ggagaaggat	gggtccacca	gtgggggggtc	accgtcgggg	cccaagtcgc	1080
tacggcccc	agtatgggca	ccccccaccc	cctccccac	caccgagta	tggccctcac	1140
gccgacagcc	ctgtgctcat	ggtctatggc	ttggatcaat	ctaagatgaa	cggtgaccga	1200
gtcttcaatg	tcttctgctt	atatggcaat	gtggagaagg	tgaaattcat	gaaaagcaag	1260
ccggggggcg	ccatggtgga	gatggctgat	ggctacgctg	tagaccgggc	cattaccac	1320
ctcaacaaca	acttcatgtt	tgggcagaag	ctgaatgtct	gtgtctccaa	gcagccagcc	1380
atcatgcctg	gtcagtcata	cgggttgga	gacgggtctt	gcagttacaa	agacttcagt	1440
gaatcccga	acaatcggtt	ctccacccca	gagcaggcag	ccaagaaccg	catccagcac	1500
cccagcaacg	tgctgcactt	cttcaacgcc	ccgctggagg	tgaccgagga	gaacttcttt	1560
gagatctgcg	atgagctggg	agtgaagcgg	ccatcttctg	tgaaagtatt	ctcaggcaaa	1620
agtgagcgca	gctcctctgg	actgctggag	tgggaatcca	agagcgatgc	cctggagact	1680
ctgggcttcc	tgaaccatta	ccagatgaaa	aacccaaatg	gtccataccc	ttacactctg	1740
aagttgtgtt	tctccactgc	tcagcacgcc	tcctaattag	gtgcctagga	agagtcccat	1800
ctgagcagga	agacatttct	ctttccttta	tgccattttt	tgtttttgtt	atttgcaaaa	1860
gatcttgtat	tccttttttt	tttttttttt	tttttttaa	gctaggtttg	tagaggctta	1920
cttaacctta	atggaaacgc	tggaaatctg	cagggggagg	gaaaggggaa	ctgttatctc	1980
ccaagattaa	ccttcacttt	taaaaaatta	ttggacatgt	gaattttttt	tttcctgggtc	2040
atacatttgg	gctgccccatg	tactcttggc	ccatttcaat	aaaattgttt	ggaaaat	2097

Information for SEQ ID No: # 56
 SEQUENCE CHARACTERISTICS
 Length: 2243
 Type: DNA
 ORIGINAL SOURCE: Homo sapiens

Feature
 Name/Key: misc_feature
 Location: (72)
 Other Information: n is A or G or C or T

Feature
 Name/Key: polyA_site
 Location: (2243)

SEQUENCE DESCRIPTION: SEQ ID NO: 56

atggcggtcca	tgcgggagag	cgacacgggc	ctgtggctgc	acaacaagct	ggggggccacg	60
gacgagctgt	angcgccgcc	cagcatcgcg	tccctgctca	cggccgcaat	catcgacaac	120
atccgtctct	gcttccatgg	cctctcgctg	gcgtccctgc	tcacggccgc	ggcatcgcac	180
aacatccgtc	tctgcttcca	tggcctctcg	tcggcagtga	agctcaagtt	gctactcggg	240
acgctgcacc	tcccgcgccc	cacggtggac	gagatgaagg	gcgccctaata	ggagatcatc	300
cagctcgcca	gcctcgactc	ggaccccctgg	gtgctcatgg	tcgccgacat	cttgaagtcc	360
tttccggaca	caggctcgct	taacctggag	ctggaggagc	agaatcccaa	cgttcaggat	420
attttgggag	aacttagaga	aaaggtgggt	gagtgtgaag	cgtctgccat	gctgccactg	480
gagtgccagt	acttgaacaa	aaacgccctg	acgaccctcg	cgggaccctc	cactcccccg	540
gtgaagcatt	ttcagttaaa	gcggaaaccc	aagagcgcca	cgctgcgggc	ggagctgctg	600
cagaagtcca	cggagaccgc	ccagcagttg	aagcggagcg	ccgggggtgcc	cttcacagcc	660
aagggccggg	ggctgctgcg	gaagatggac	accaccaccc	cactcaaagg	catcccgaag	720
caggcgccct	tcagaagccc	cacggcgccc	agcgtcttca	gccccacagg	gaaccggacc	780
cccatcccgc	cttcaggagc	gctgctgctg	aaggaacgag	gtgtgaagct	gctggacatc	840
tctgagctgg	atatggttgg	cgctggccga	gaggcgaagc	ggagaaggaa	gactctcgat	900
gcggaggtgg	tggagaagcc	ggccaaggag	gaaacggtgg	tggagaacgc	caccccgagc	960
tacgcagccg	gcctggtgtc	cacgcagaaa	cttgggtccc	tgaacaatga	gcctgcgctg	1020
ccctccacga	gctaccttcc	ctccacgccc	agcgtggttc	ccgcctcctc	ctacatcccc	1080
agctccgaga	cgccccccagc	cccatcttcc	cgggaaagcca	gccgcccacc	agaggagccc	1140
agcgccccga	gccccacggt	gccagcgagc	ttcaagcagc	gggcgcccac	gtacaacagc	1200
ggcctgagcc	ctgccacacc	cacgcctgcg	gcgcccacct	cgctcttgac	accaccacca	1260
cctccggctg	tcgcccctac	cactcagaca	cccccggttg	ccatggtggc	cccgagacc	1320
caggccccctg	ctcagcagca	gcctaagaag	aacctgtccc	tcacgagaga	gcagatgttc	1380
gctgcccagg	agatgttcaa	gacggccaac	aaagtacgcg	ggcccagaaa	ggccctcatc	1440
ctgggcttca	tggccggctc	ccgagagaac	ccgtgccagg	agcaggggga	cgtgatccag	1500
atcaagctga	gcgagcacac	ggaggacctg	cccaaggcgg	acggccaggg	tagcacaacc	1560
atgctggtgg	acacagtgtt	tgagatgaac	tatgccacgg	gccagtggac	gcgcttcaag	1620
aagtacaagc	ccatgaccaa	tgtgtcctag	aaccacctgc	ctcacagctg	gccgtcactt	1680
gtgggggtcc	acgggacgat	ggctttgcc	gcttaaagta	accggatggc	ggacacctgg	1740
cccccgaggt	cccccgggcg	ccgcccctgt	gctgacctag	cctgttttta	gttctggatg	1800
catttctctg	gggtatttgg	ggcttatttt	taaaatttta	atatgggttc	ttttttgtgt	1860
gatttaagac	acttttttga	ctcaacgtta	cattttttgaa	tgtagtaagt	aaattaacca	1920
aaaaagttac	aacttcctaa	tttttagtgac	agctctgcct	gttagactct	tactttttta	1980
aatcttttct	attttccctc	gctggggcag	tgccctccta	ccccaggggt	tgaggggacc	2040
aaggtggcac	ggtggtactg	ggggtgcggc	agggacaccc	gaccacacca	gagcgtggga	2100
gacggtgggc	cttgtcccct	gcctgtgcct	gcctgggagt	tttgtattca	tcttttgtat	2160
agttgtggac	atttaagaca	gtctttgggt	acctattttc	attgtaaaac	tatctgaacc	2220
attaaagtcg	agcttttcta	aag				2243

Information for SEQ ID No: # 57
 SEQUENCE CHARACTERISTICS
 Length: 831
 Type: DNA
 ORIGINAL SOURCE: Homo sapiens

Feature
 Name/Key: polyA_site
 Location: (831)

SEQUENCE DESCRIPTION: SEQ ID NO: 57

gcgggagggc	agcgagaggt	tcgcgggtgc	agcgcacagg	agaccatgtc	cgggggcagc	60
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agctgcagcc agaccccaag ccggggccatc cccgccactc gccgggtggt gctcggcgac 120
ggcgtgcagc tcccggcccg ggactacagc acgacccccc gcggcacgct cttcagcacc 180
accccgggag gtaccaggat catctatgac cggaaattcc tgatggagtg tcggaactca 240
cctgtgacca aaacaccccc aagggatctg cccaccattc cgggggtcac cagcccttcc 300
agtgatgagc ccccatgga agccagccag agccacctgc gcaatagccc agaagataag 360
cgggcgggcg gtgaagagtc acagtttgag atggacattt aaagcaccag ccatcgtgtg 420
gagcactacc aaggggcccc tcagggcctt cctgggagga gtcccaccag ccaggcctta 480
tgaaagtgat catactgggc aggcgttggc gtggggtcgg acaccccagc cttttctccc 540
tcactcaggg cacctgcccc ctctctcttc tgaacaccag cagatacctc cttgtgcctc 600
cactgatgca ggagctgcca cccaagggg agtgaccctt gccagcacac cctgcagcca 660
agggccagga agtggacaag aacgaaccct tccttccgaa tgatcagcag ttccagcccc 720
tcgctgctgg gggcgcaacc accccttcct taggttgatg tgcttgggaa agctccctcc 780
ccctccttcc ccaagagagg aaataaaaagc caccttcgcc ctagggccaa g 831

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Information for SEQ ID No: # 58

SEQUENCE CHARACTERISTICS

Length: 2404

Type: DNA

ORIGINAL SOURCE: Homo sapiens

SEQUENCE DESCRIPTION: SEQ ID NO: 58

```

cacgcgtaag cttgggcccc tcgagggatc ctctagagcg gccgccgaga cgtccccggc 60
acgctgatgg agcccgggcg cggcgcgggg cccgcgggca tggcgaggcc tcgggcgaag 120
gcggcgcggc cggggcccca gcgctttctg cggcgcgagc tggtagagtc ggaccaggag 180
gagccgcccg gcttgaggcg agccgaggcg ccgggccccg agcccccgca gcccctgcag 240
cgccgggtgc ttctgctctg caagacgcgc cgctcatcg cggagcgcg cgcggacgc 300
cccgccgccc ccgcgcccgc agcgtggta gcgcagccgg gagcccccg agcccccgcg 360
gacgccggcc ccgagcccgt gggcacgcag gagcccggcc cggaccccat cgcagccgct 420
gtcgaaacgg cgctgcccc cgacggcggc cccagggagg aggcggcggc taccgtgagg 480
aaggaggatg agggggcggc cgaggcgaag cctgagcccg ggcgcaactc ccgggacgag 540
cccgaagagg aggaggacga cgaggacgac ctcaaggccg tggccacctc tctggacggc 600
cgcttcctca agttcgacat cgagctgggc cgcggttctt tcaagacggt ctacaagggg 660
ctggacacgg agacctgggt ggaggtggcc tgggtgtgag tgcaggaccg gaagctcacc 720
aagctggagc ggcagcggtt caaggaagag gctgagatgc tgaaaggcct gcagaccccc 780
aacatcgtgc gcttctacga cttctgggag tccagcgcca agggcaagcg gtgcattgtg 840
ctggtgacgg agcttatgac ctcagggacg ctgaagacat acctgaagcg gttcaagggtg 900
atgaagccca aggttctccg cagctggtgc cggcagatcc tgaaggccct gctgttcctg 960
cacacaagga cgccacccat catccaccga gacctgaaat gtgacaatat tttcatcacc 1020
ggaccaactg ggtctgtgaa gattggcgac ttgggcctgg ccactctgaa aagagcgtca 1080
tttgccaaaa gtgtgatagg tactcccagag ttcatggcgc ccgagatgta cgaggagcac 1140
tacgatgagt ccgtggacgt ctatgccttt gggatgtgca tgctggagat ggccacctcg 1200
gagtacccct actcggagtg ccagaatgcg gccagatct accgcaaggt cacctgtggt 1260
atcaagccgg ccagctttga gaaagtgcac gatcctgaaa tcaaggagat tattggggag 1320
tgtatctgca aaaacaagga ggaaaggtag gagatcaaag acctgctgag ccacgccttc 1380
ttcgagagg acacaggcgt gaggggtggag ctcgcgagg aggaccacgg caggaagtcc 1440
accatcgccc tgaggctctg ggtggaagac cccaagaaac tgaagggaaa gcccaaggac 1500
aatggagcca tagagtccac cttcgacctg gagaaggaga cgccggatga agtggcccaa 1560
gagatgattg agtctggatt cttccacgag agtgacgtca agatcgtggc caagtccatc 1620
cgtgaccgcg tggccttgat ccagtggcgg cgggagagga tctggcccgc gctgcagccc 1680
aaggagcagc aggatgtggg cagcccggac aaggccaggg gtccgcccgt gcccctgcag 1740
gtccagggtg cctaccatgc acaggctggg cagcccgggc caccagagcc cgaggagccg 1800
gaggccgacc agcacctcct gccacctacg ttgccgacca gcgccacctc cctggcctcg 1860
gacagcacct tcgacagcgg ccagggtctt accgtgtact cagactcgca gagcagccag 1920
cagagcgtga tgcttggctc ccttgccgac gcagcgccgt ccccggccca gtgtgtgtgc 1980
agccccctg tgagcgaggg gcccgctctg ccgcagagcc tgccctcgct gggggcctac 2040
cagcagccca cggctgcacc tcctccgctg gccagccga caccctgcc gcaggtcctg 2100
gccccacagc ccgtggtccc cctccagccg gttccccccc acctgccacc gtacctggct 2160
ccagcctccc aggtgggggc ccccgctcag ctgaagcccc tccagatgcc acaggcgccc 2220
ctgcagccgc ttgctcaagt ccctccgcag atgccccga ttcctgttgt gccccccatc 2280
acgcccctgg cgggaatcga cggcctccct ccggccctcc cagacctgcc gaccgcgact 2340
gtgcctcccg tgccaccacc tcagtatttc tctccagccg tgatcttgcc gagccggacg 2400
cgtg 2404

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Information for SEQ ID No: # 59

SEQUENCE CHARACTERISTICS

Length: 6707

Type: DNA

ORIGINAL SOURCE: Homo sapiens

Feature

Name/Key: polyA_site

Location: (6707)

SEQUENCE DESCRIPTION: SEQ ID NO: 59

cccaagtttg	gggaagacag	gaactgcagc	gccccctcccc	gtttcacgcc	acgcgcggga	60
ccgaggacct	aggacctggc	cagctgggcg	tggttcggag	agccggggcg	gaaaacgaaa	120
ccagaaatcc	gaaggccgcg	ccagagccct	gcttccccctt	gcatctgcgc	cgggaggcca	180
tggacttgta	cagcaccctg	gccgctgcgc	tggacagggt	cgtggccaga	aagctgcagc	240
cgcggaagga	gttcgtagag	aaggcgcggc	gcgctctggg	cgccctggcc	gctgctctga	300
gggagcgcg	gggcccgcctc	ggtgctgctg	ccccgcgggt	gctgaaaact	gtcaagggag	360
gctcctcggg	ccggggcaca	gctctcaagg	gtggctgtga	ttctgaactt	gtcatcttcc	420
tcgactgctt	caagagctat	gtggaccaga	gggcccgcgc	tgcagagatc	ctcagtgaga	480
tgcgggcata	gctggaatcc	tgggtggcaga	acccagtcct	tggctctgaga	ctcacgtttc	540
ctgagcagag	cgtgcctggg	gccctgcagt	tccgcctgac	atccgtagat	cttgaggact	600
ggatggatgt	tagcctgggtg	cctgccttca	atgtcctggg	tcaggccggc	tccggcgtca	660
aacccaagcc	acaagtctac	tctaccctcc	tcaacagtgg	ctgccaaggg	ggcgagcatg	720
cggcctgctt	cacagagctg	cggaggaact	ttgtgaacat	tcgcccagcc	aagttgaaga	780
acctaattctt	gctggtgaag	cactggtacc	accaggtgtg	cctacagggg	ttgtggaagg	840
agacgctgcc	cccggcttat	gccctggaat	tgttgaccat	cttcgcctgg	gagcagggct	900
gtaagaagga	tgctttcagc	ctagccgaag	gcctccgaac	tgtcctgggc	ctgatccaac	960
agcatcagca	cctgtgtgtt	ttctggactg	tcaactatgg	cttcgaggac	cctgcagttg	1020
ggcagttctt	gcagcggcag	cttaagagac	ccaggcctgt	gatcctggac	ccagctgacc	1080
ccacatggga	cctgggggaat	ggggcagcct	ggcactggga	tttgctagcc	caggaggcag	1140
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ctgtgtattt	catctattgc	caacatttca	tataaatggc	atcatac		6707

Information for SEQ ID No: # 60

SEQUENCE CHARACTERISTICS

Length: 769

Type: DNA

ORIGINAL SOURCE: Homo sapiens

Feature

Name/Key: polyA_site

Location: (769)

SEQUENCE DESCRIPTION: SEQ ID NO: 60

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tgcgtcgggc	agacttccac	gtgggtgccc	acgtgaacac	gttctggagg	accccgtgcc	300
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```

Information for SEQ ID No: # 61

SEQUENCE CHARACTERISTICS

Length: 2039

Type: DNA

ORIGINAL SOURCE: Homo sapiens

Feature

Name/Key: polyA_site

Location: (2039)

SEQUENCE DESCRIPTION: SEQ ID NO: 61

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Information for SEQ ID No: # 62

SEQUENCE CHARACTERISTICS

Length: 1822

Type: DNA

ORIGINAL SOURCE: Homo sapiens

Feature

Name/Key: polyA_site

Location: (1822)

SEQUENCE DESCRIPTION: SEQ ID NO: 62

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cggcctgcag ctgcgaggcg ccgcgtagcc gtcgccaccg ccgccagccc gtgcgccctc 60
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aaatgttttt	tttgtttttc	ag				1822

Claims

1. A peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 44 in the sequence listing.
2. A polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 45 to SEQ ID NO: 47 and SEQ ID NO: 49 to SEQ ID NO: 52 in the sequence listing.
3. A medicament comprising one or more of peptides or polypeptides, said peptides selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 44, and said polypeptides selected from the group consisting of SEQ ID NO: 45 to SEQ ID NO: 47 and SEQ ID NO: 49 to SEQ ID NO: 52 in the sequence listing.
4. An anti-cancer vaccine comprising one or more of peptides or polypeptides, said peptides selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 44, and said polypeptides selected from the group consisting of SEQ ID NO: 45 to SEQ ID NO: 47 and SEQ ID NO: 49 to SEQ ID NO: 52 in the sequence listing, for treatment of pancreatic cancer, colon cancer or stomach cancer.
5. An inducer of cytotoxic T lymphocytes comprising one or more of peptides or polypeptides, said peptides selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 44, and said polypeptides selected from the group consisting of SEQ ID NO: 45 to SEQ ID NO: 47 and SEQ ID NO: 49 to SEQ ID NO: 52 in the sequence listing.

6. A polynucleotide encoding a peptide or polypeptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 47 and SEQ ID NO: 49 to SEQ ID NO: 52 in the sequence listing, or the complementary strand thereof.

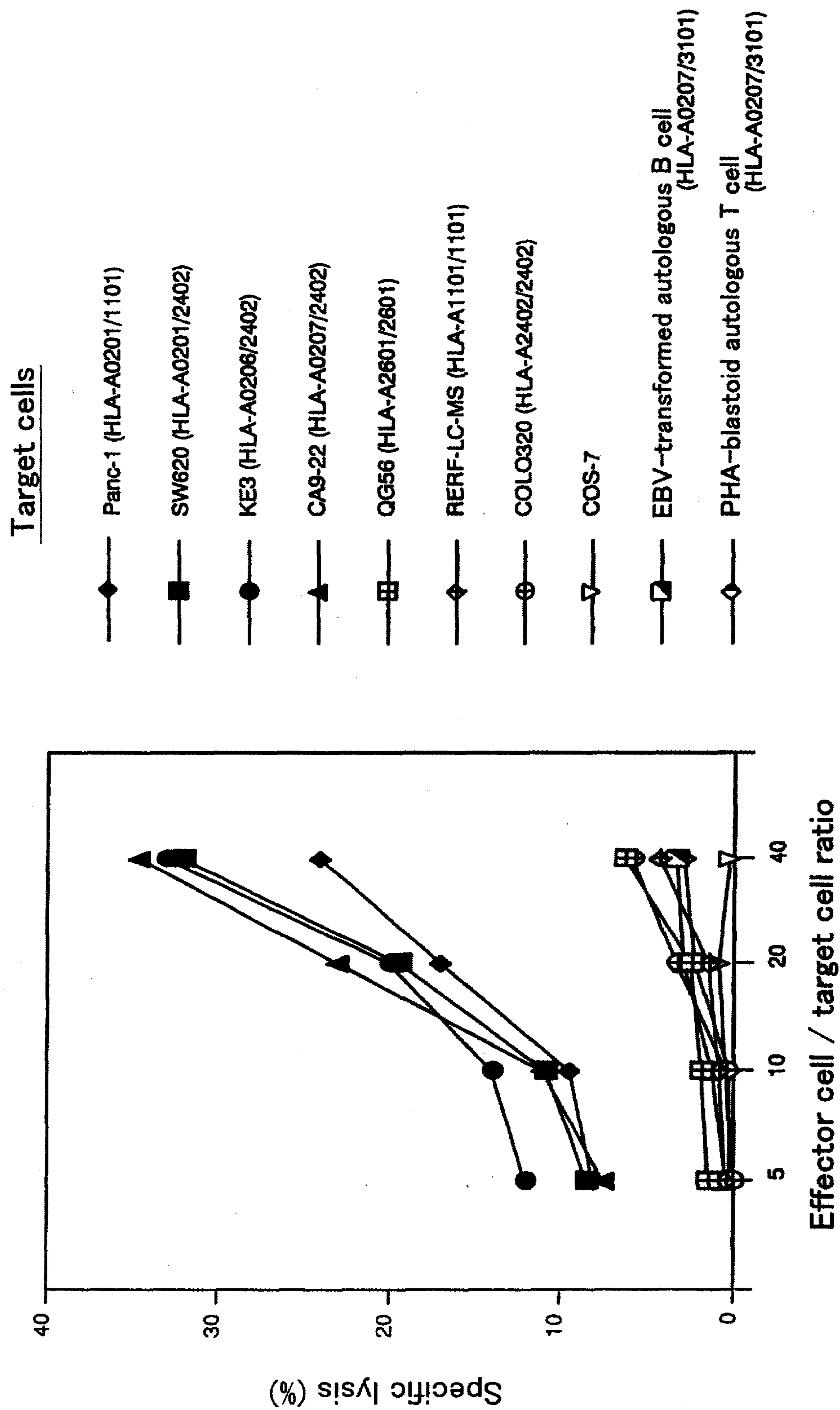
7. A polynucleotide selected from the group consisting of SEQ ID NO: 54 to SEQ ID NO: 56 and SEQ ID NO: 58 to SEQ ID NO: 61 in the sequence listing, or the complementary strand thereof, wherein a polypeptide encoded by the polynucleotide induces cytotoxic T lymphocytes and/or is recognized by cytotoxic T lymphocytes.

8. An antibody that specifically binds the peptide according to claim 1 or the polypeptide according to claim 2.

9. Use of the medicament according to claim 3, the anti-cancer vaccine according to claim 4, or the inducer of the cytotoxic T lymphocytes according to claim 5 for treatment of pancreatic cancer, colon cancer or stomach cancer.

Drawings

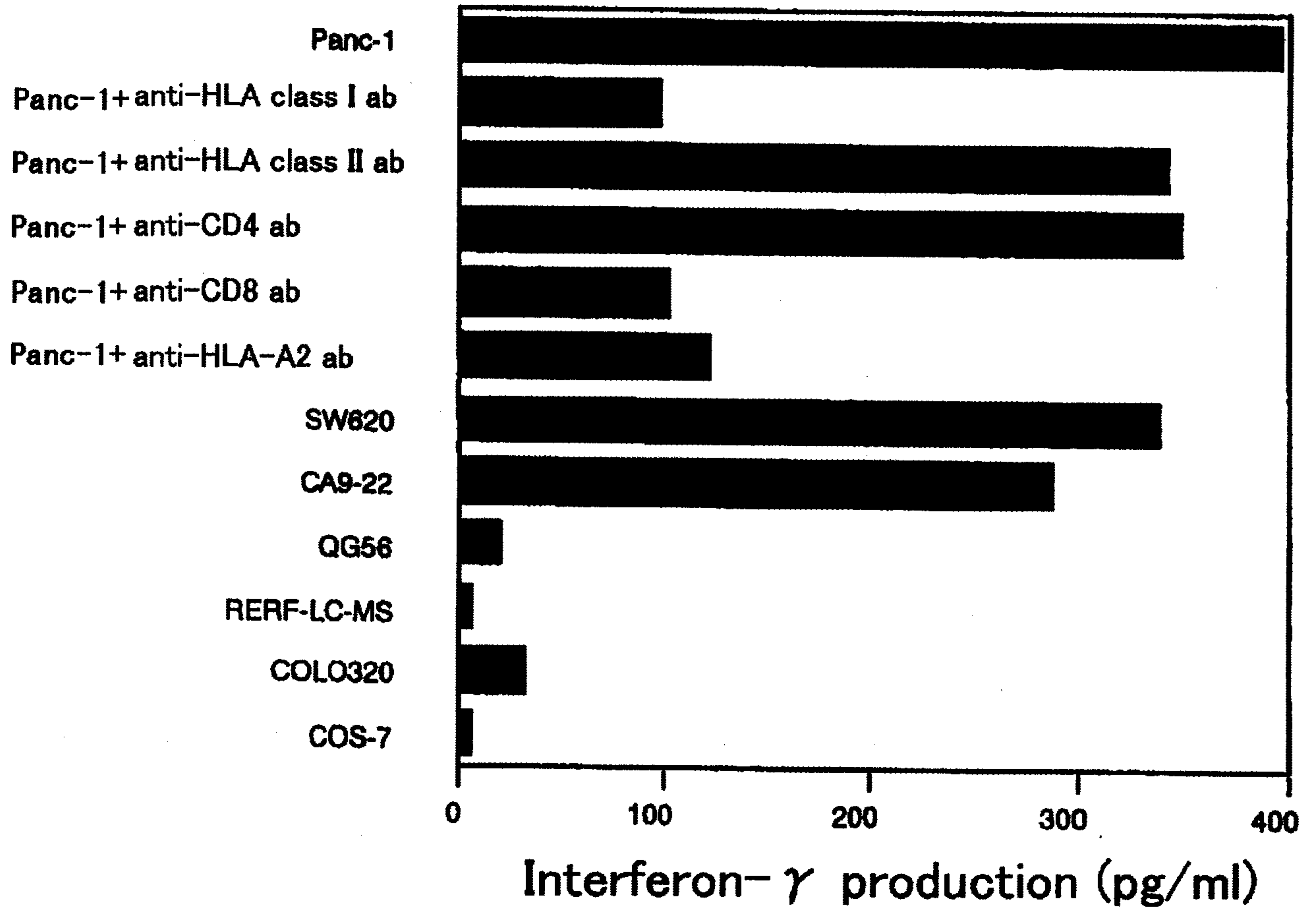
Figure 1



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Figure 2

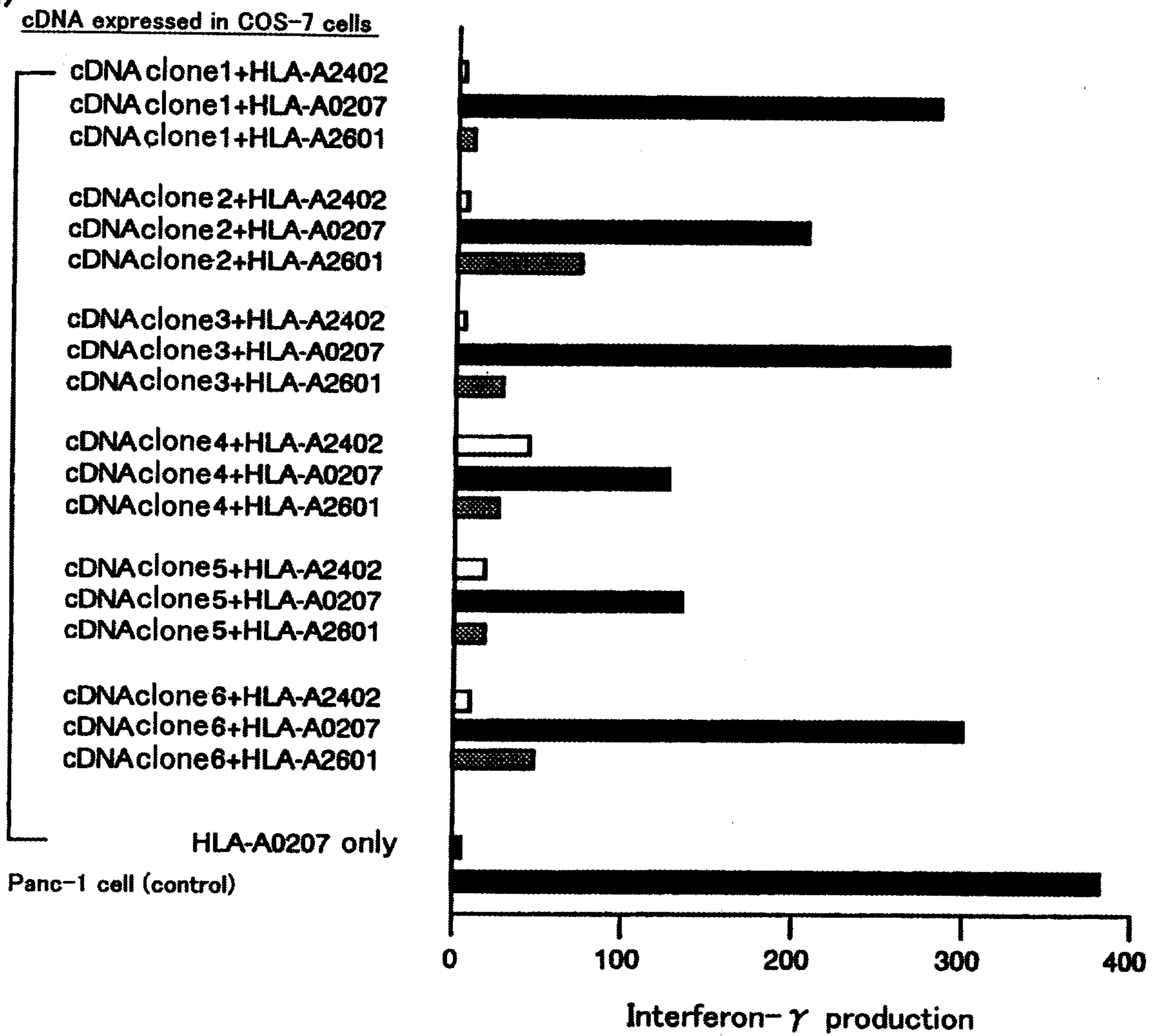
Stimulator cells



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Figure 3

(A)



(B)

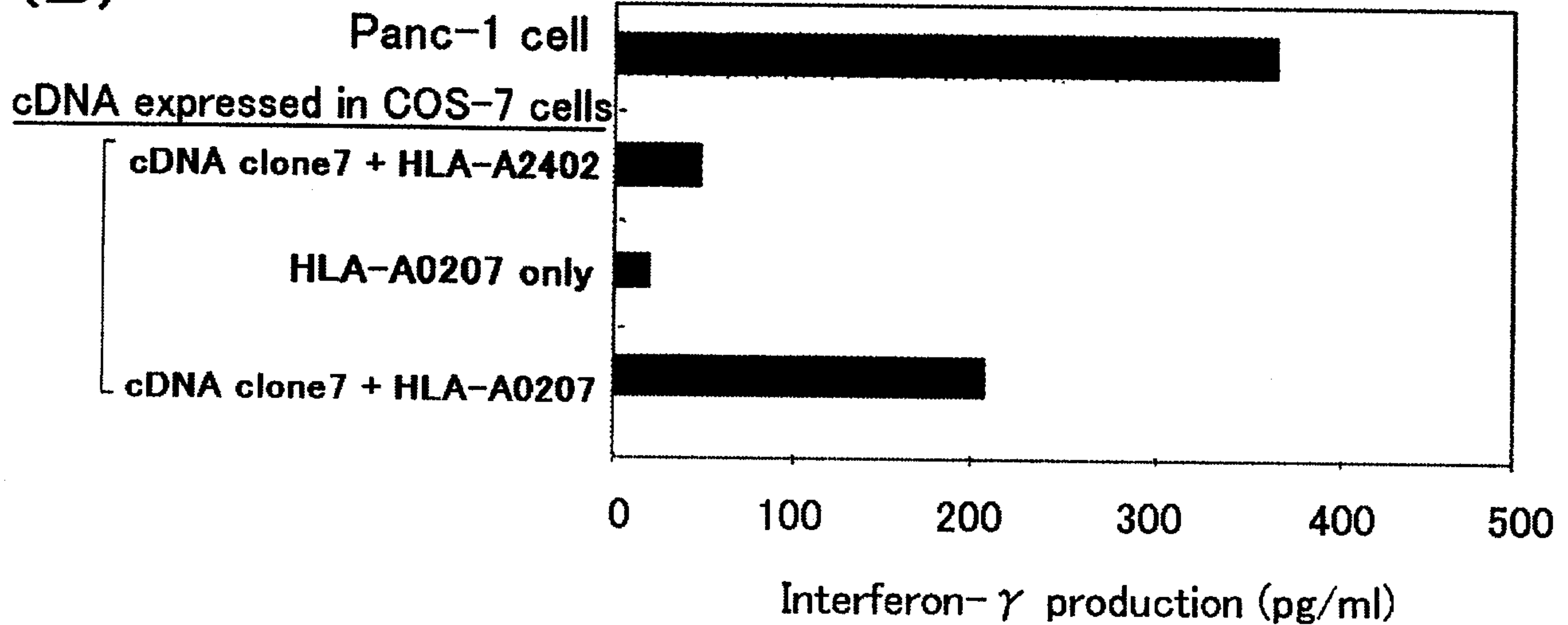
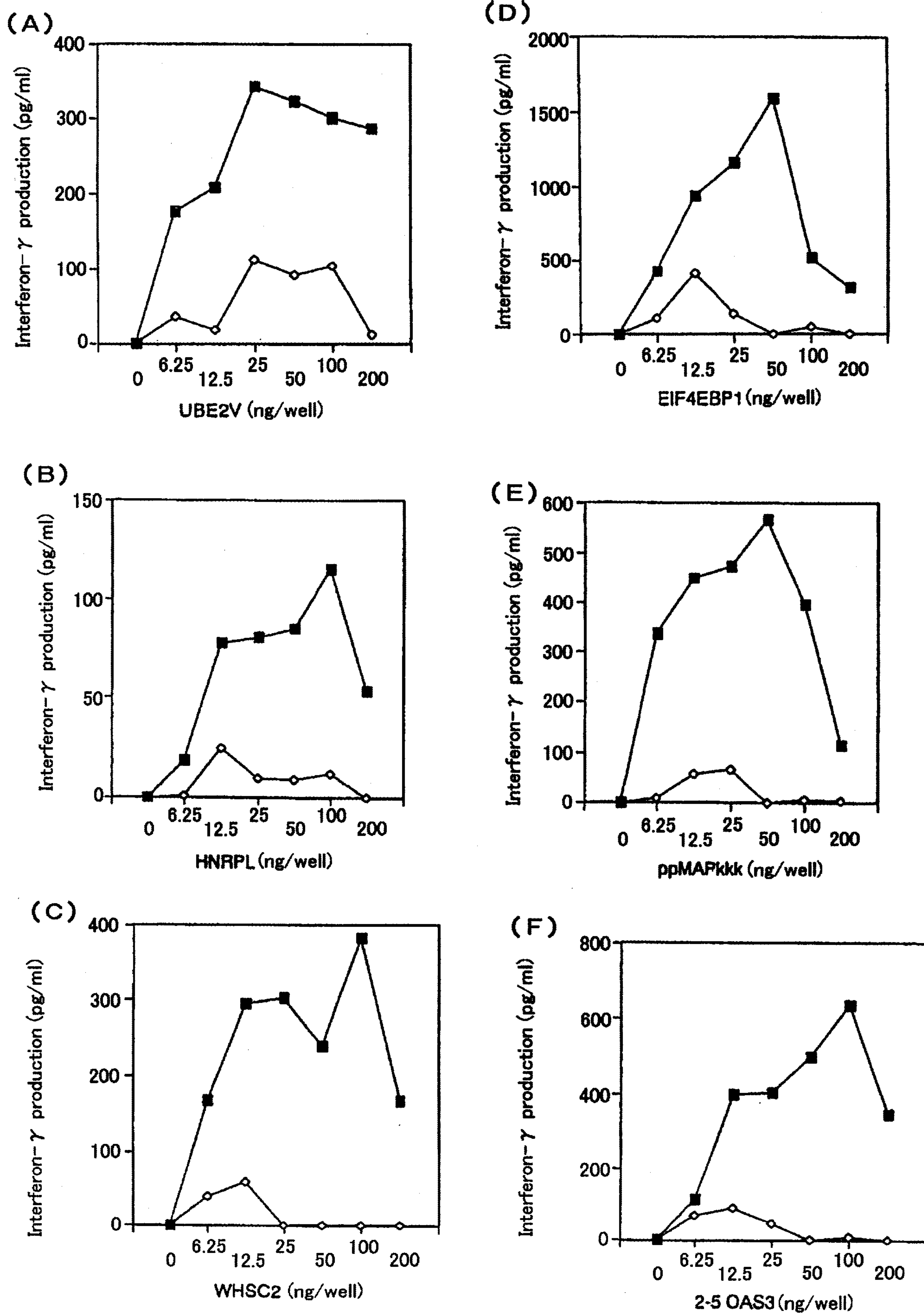
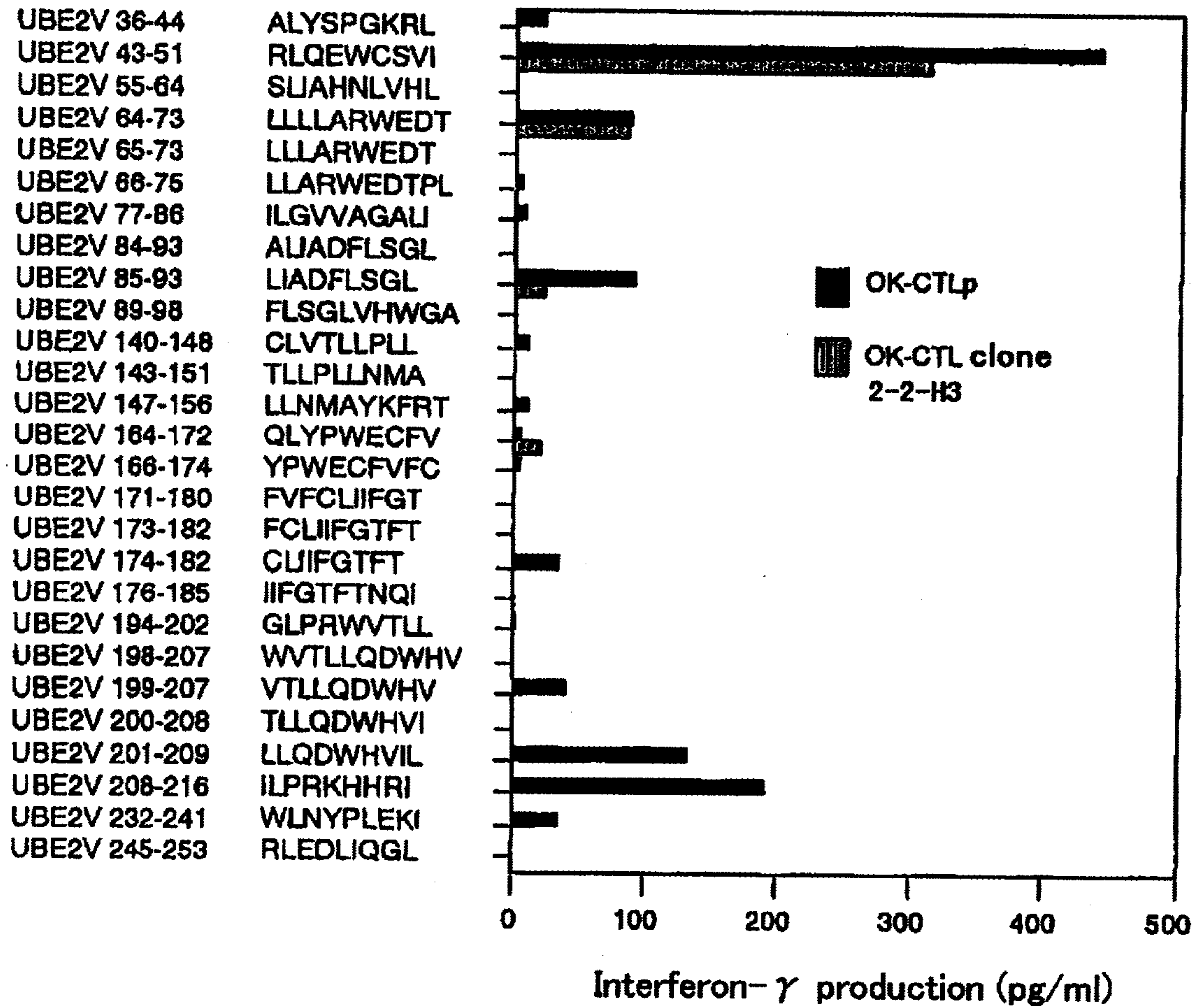


Figure 4



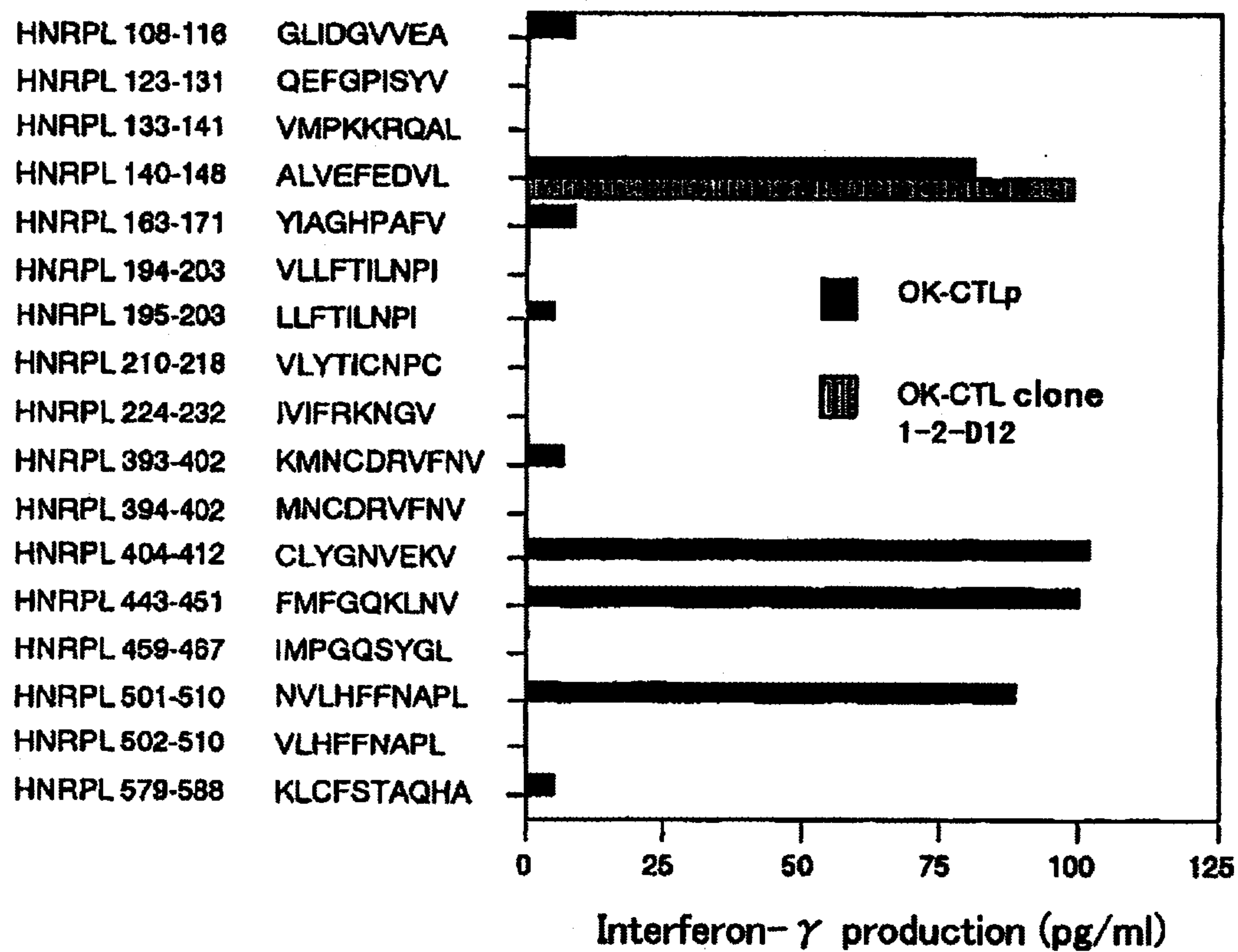
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Figure 5



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Figure 6



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Figure 7

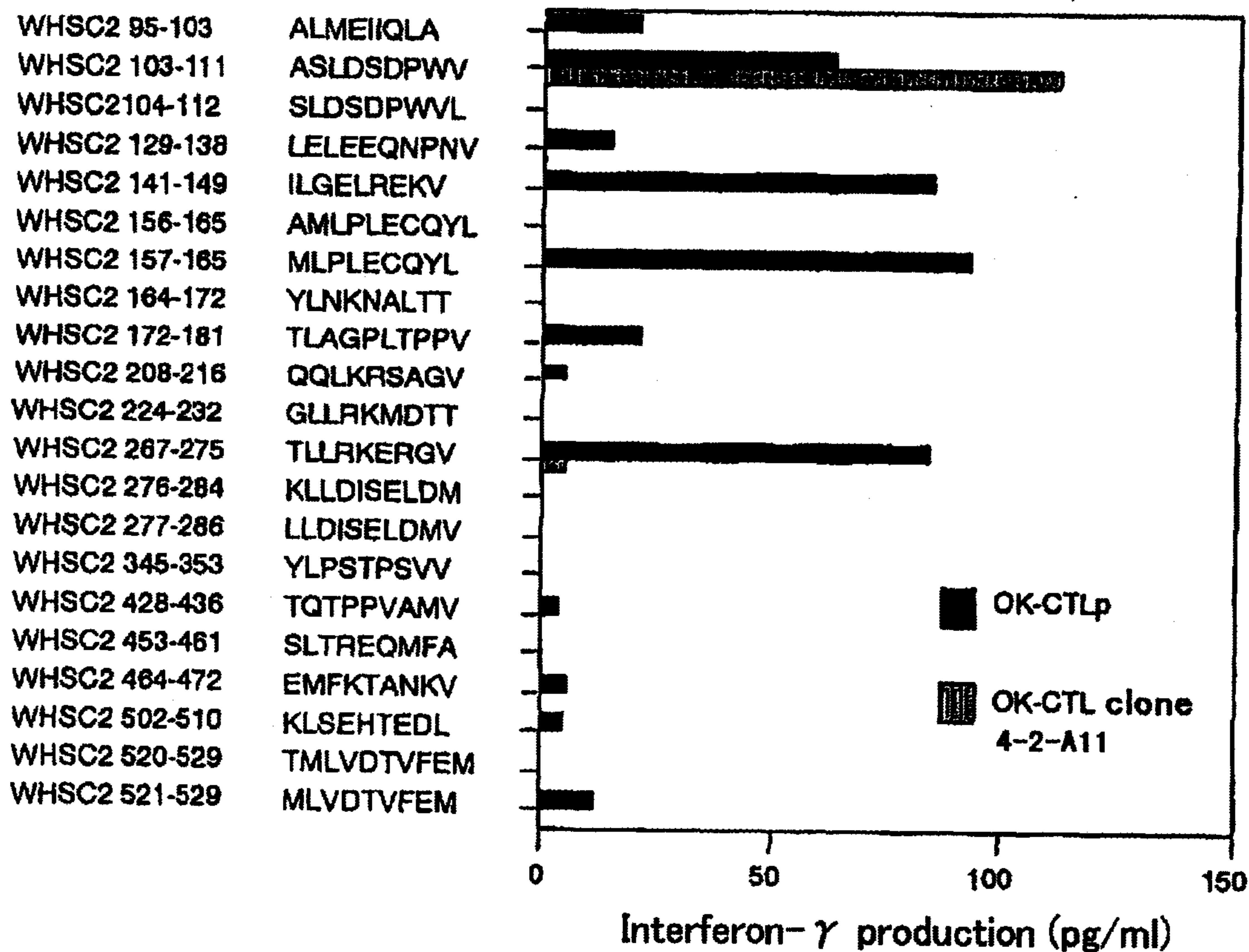
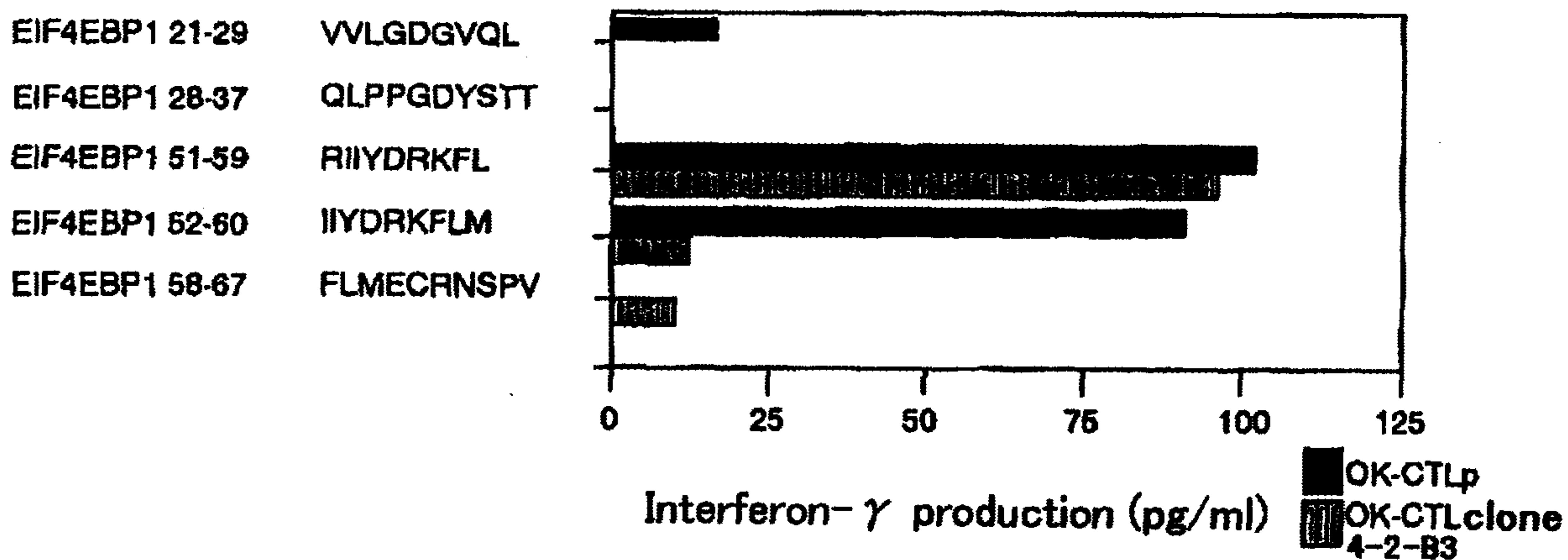


Figure 8



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Figure 9

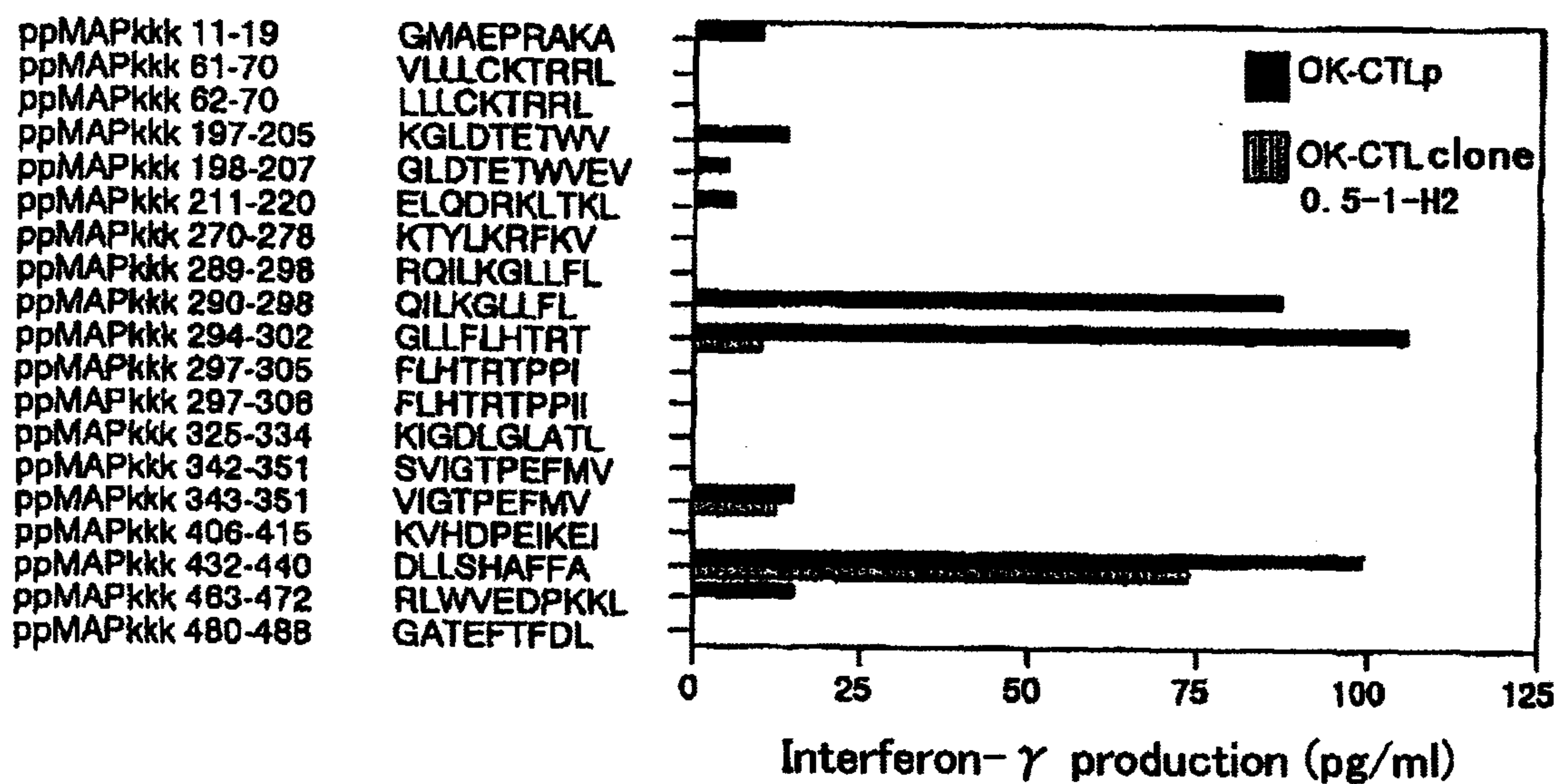


Figure 10

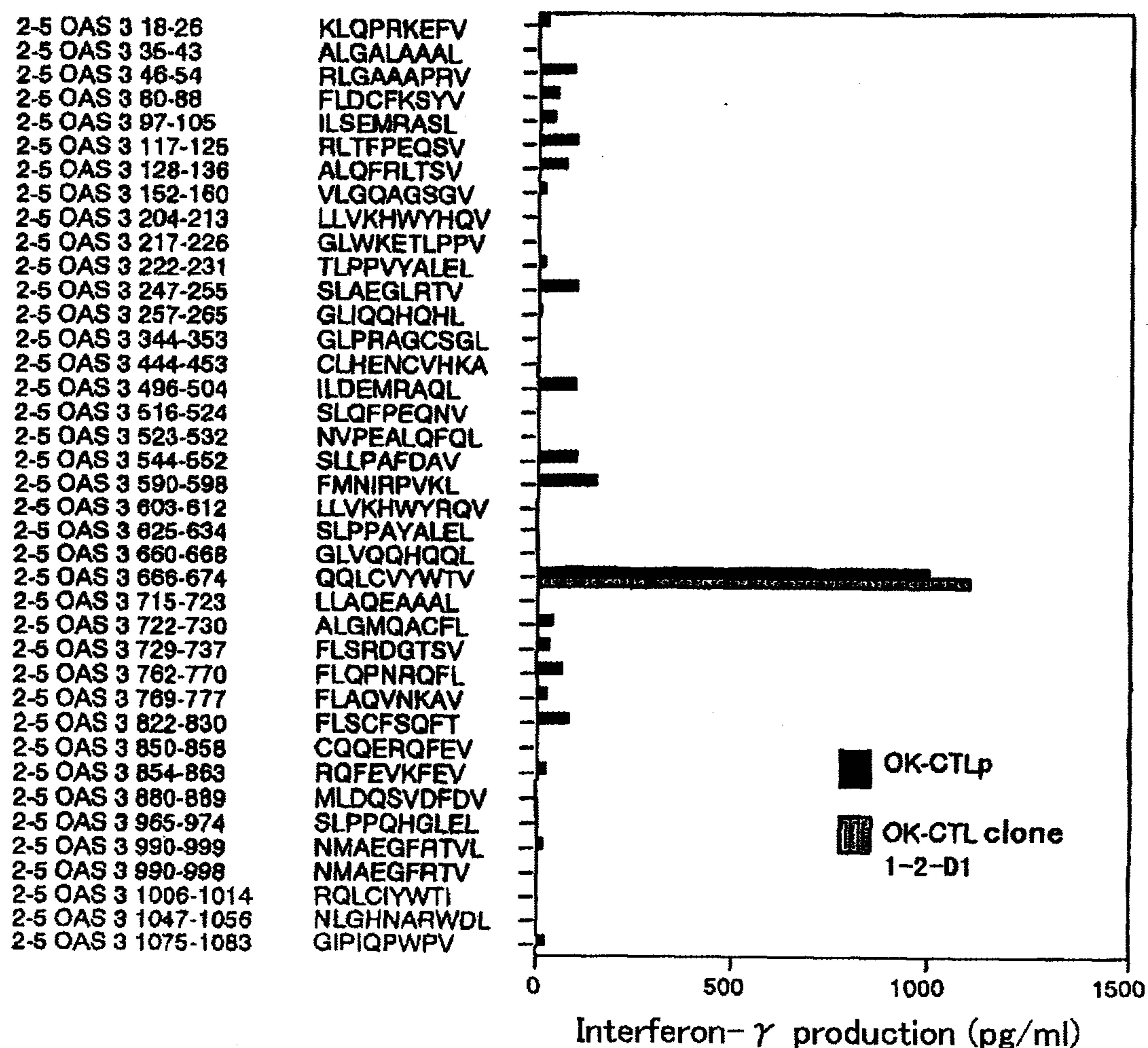
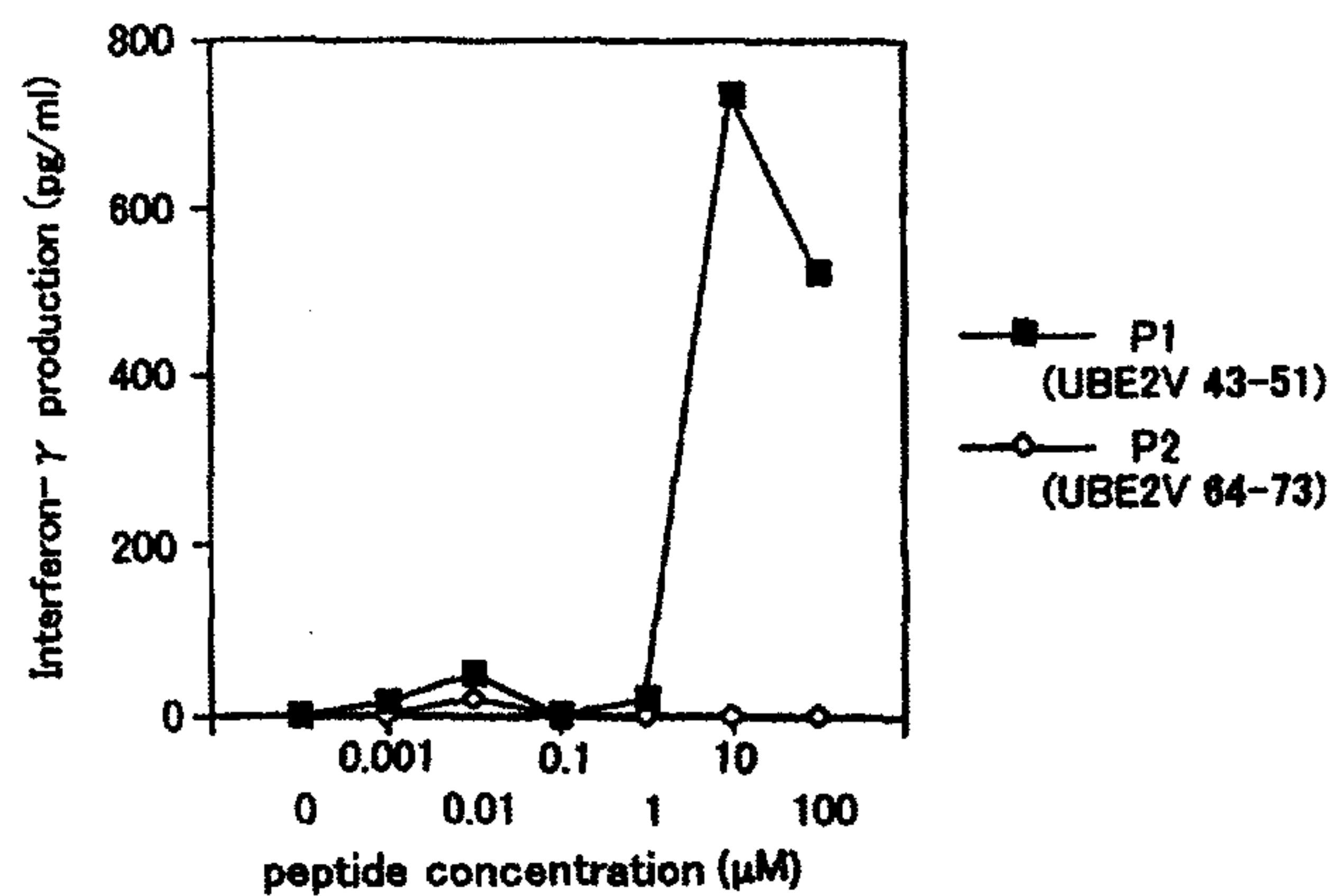
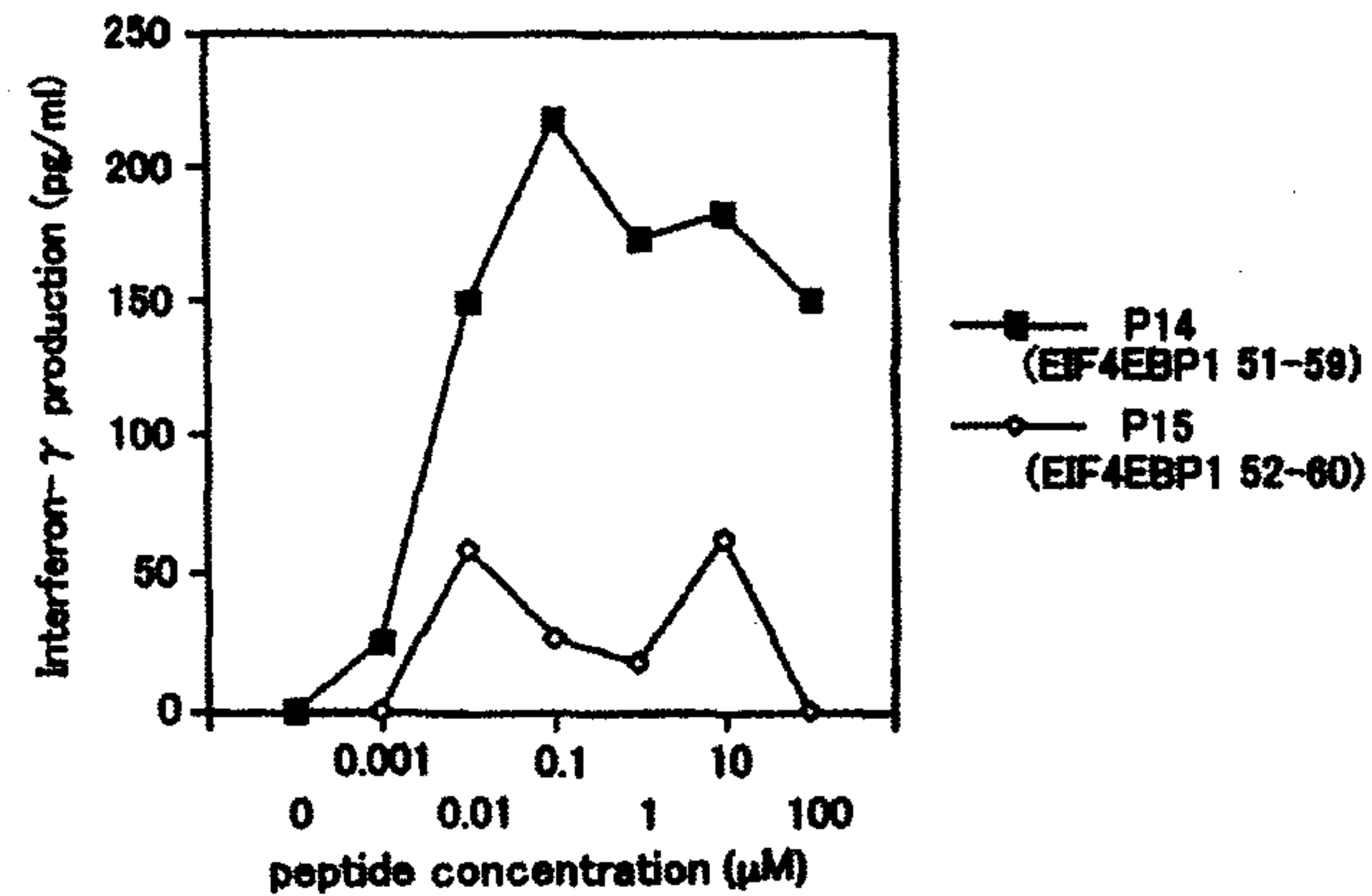


Figure 11

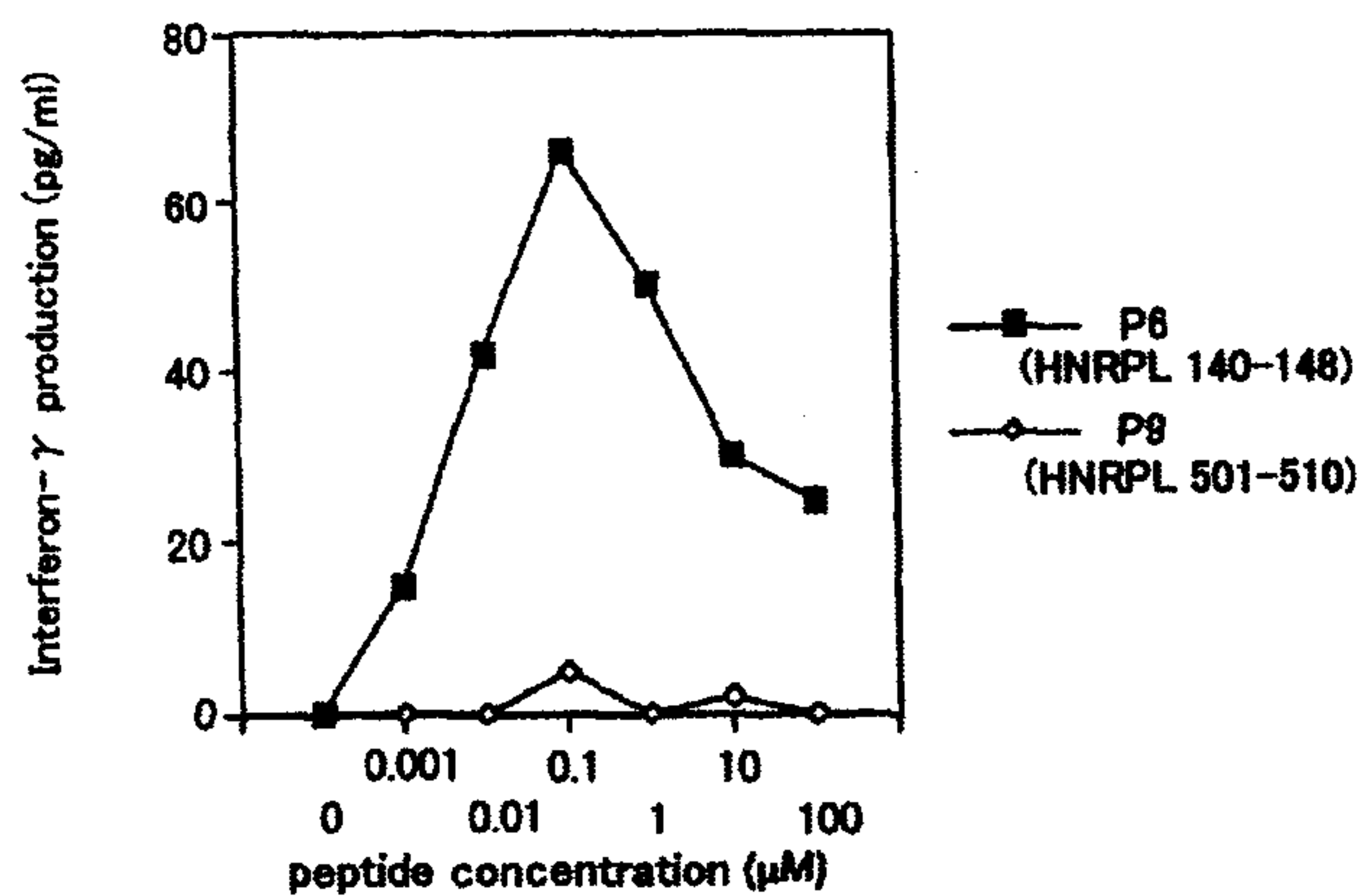
(A)



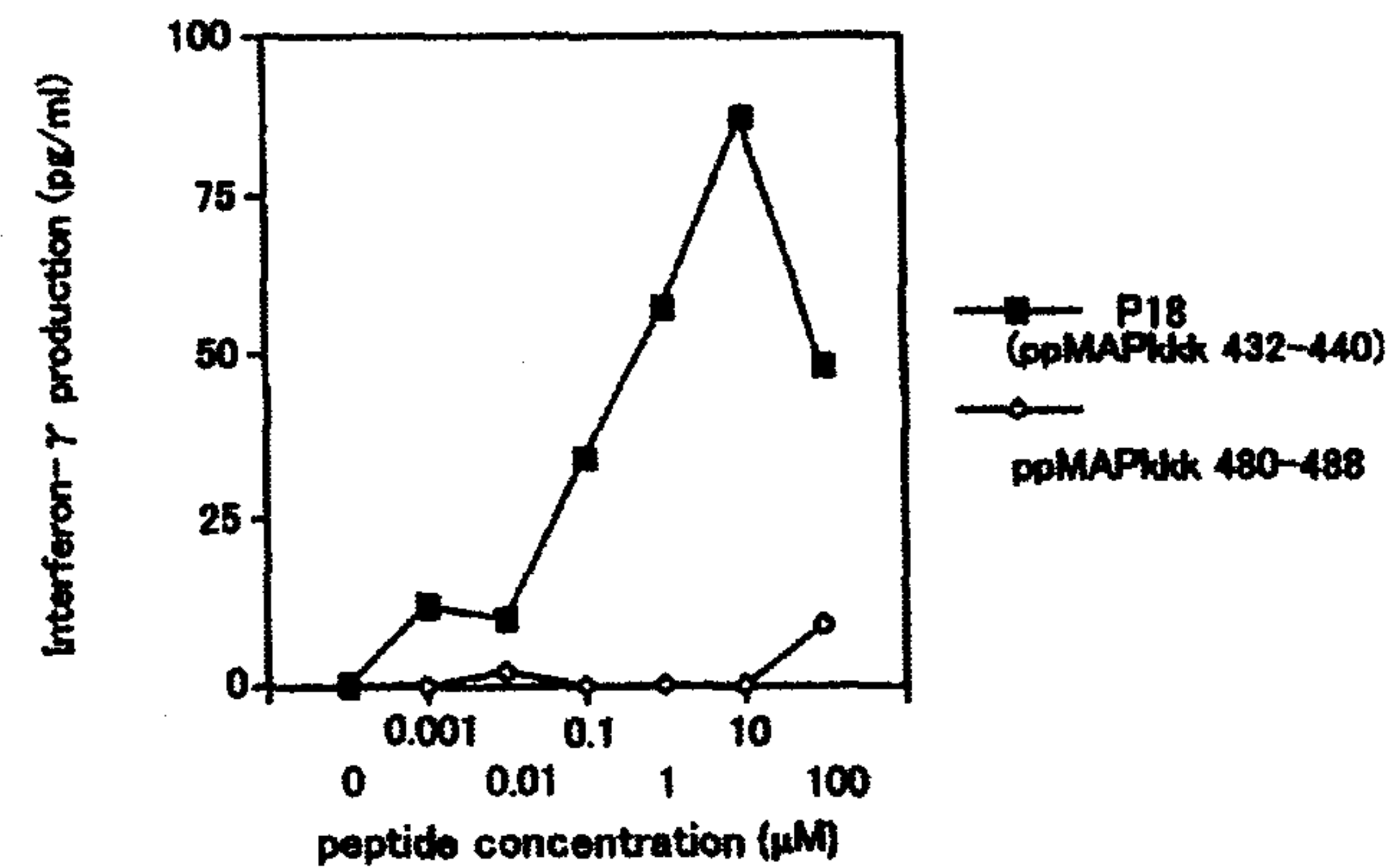
(D)



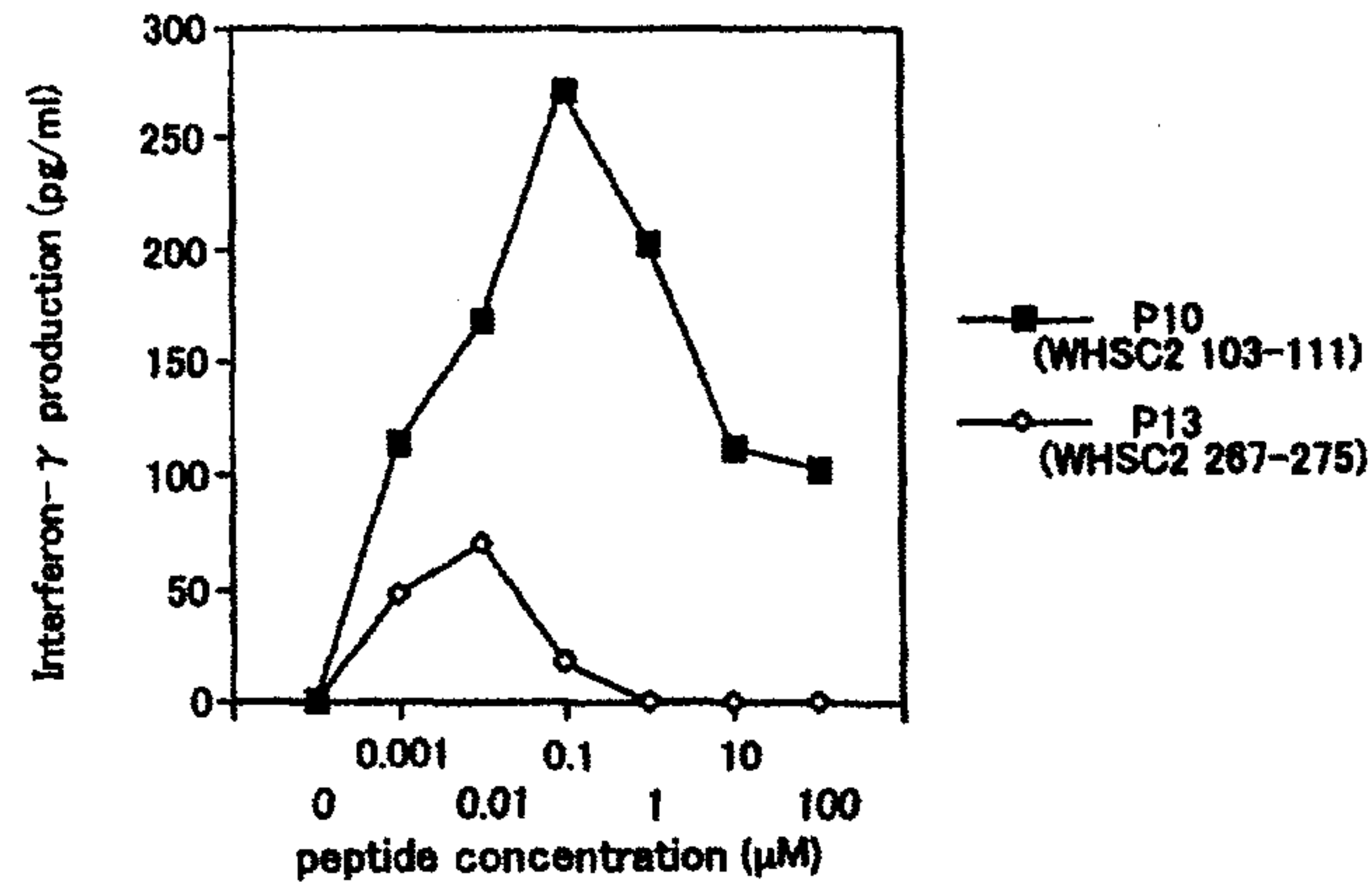
(B)



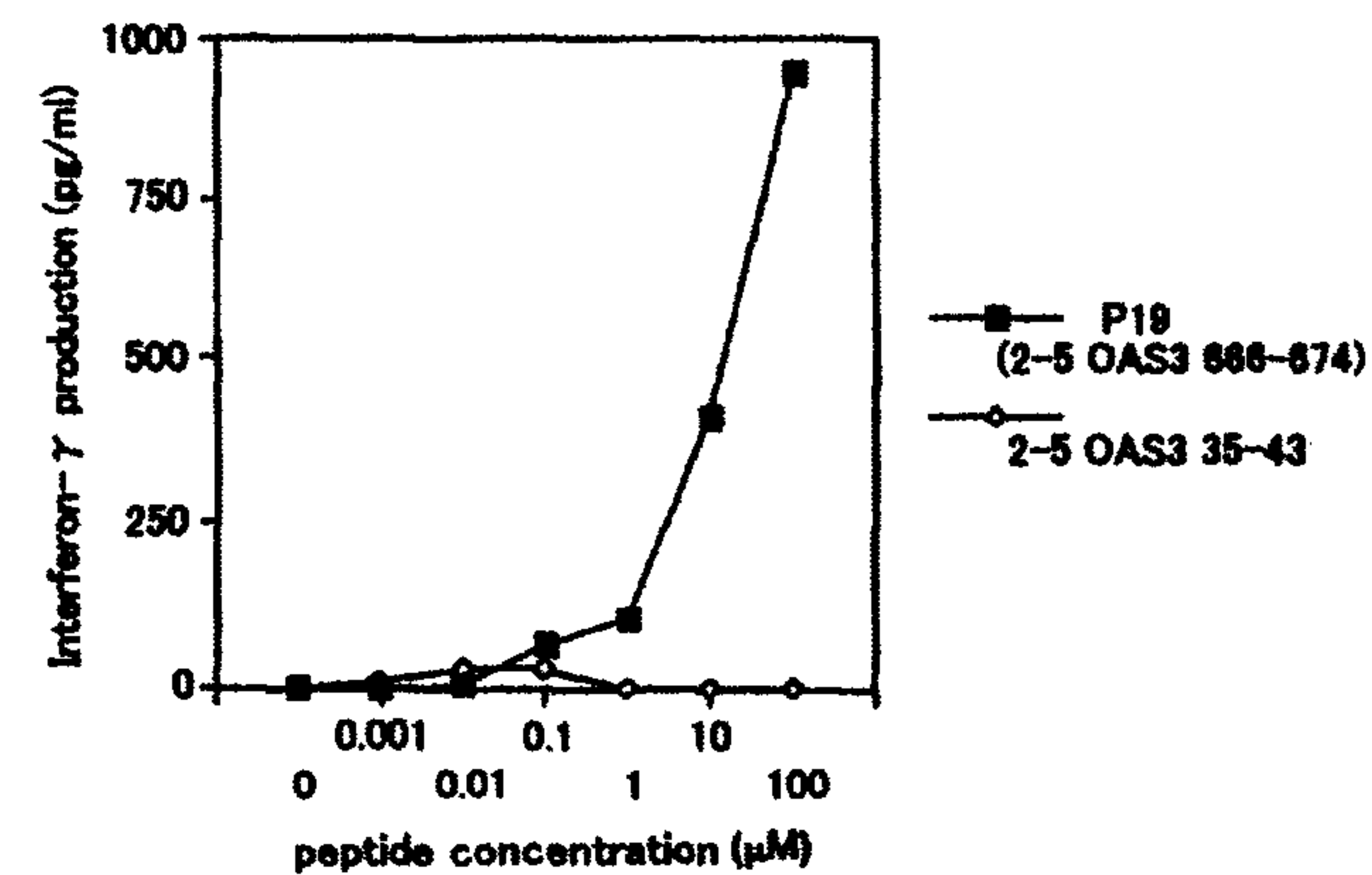
(E)



(C)



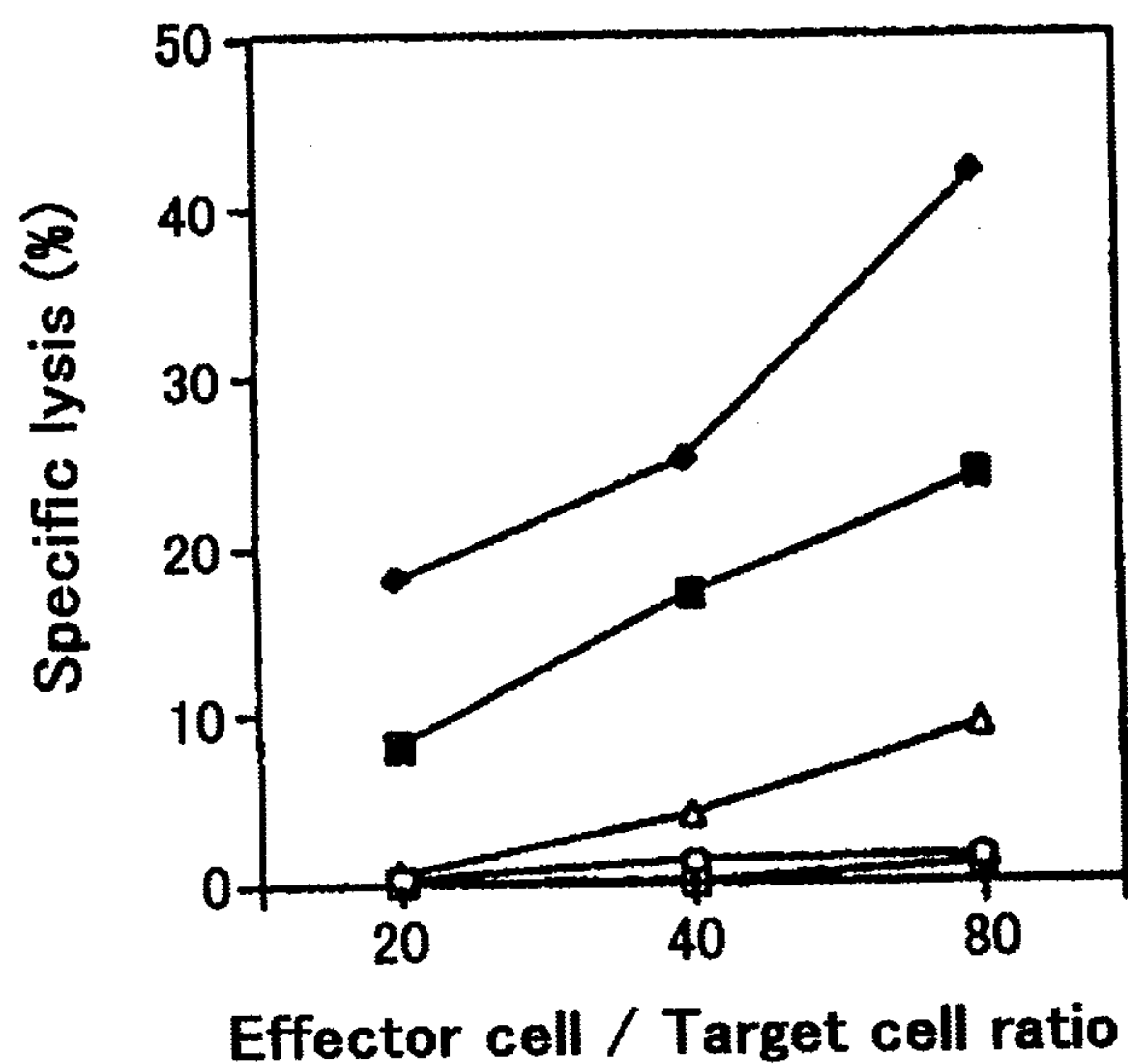
(F)



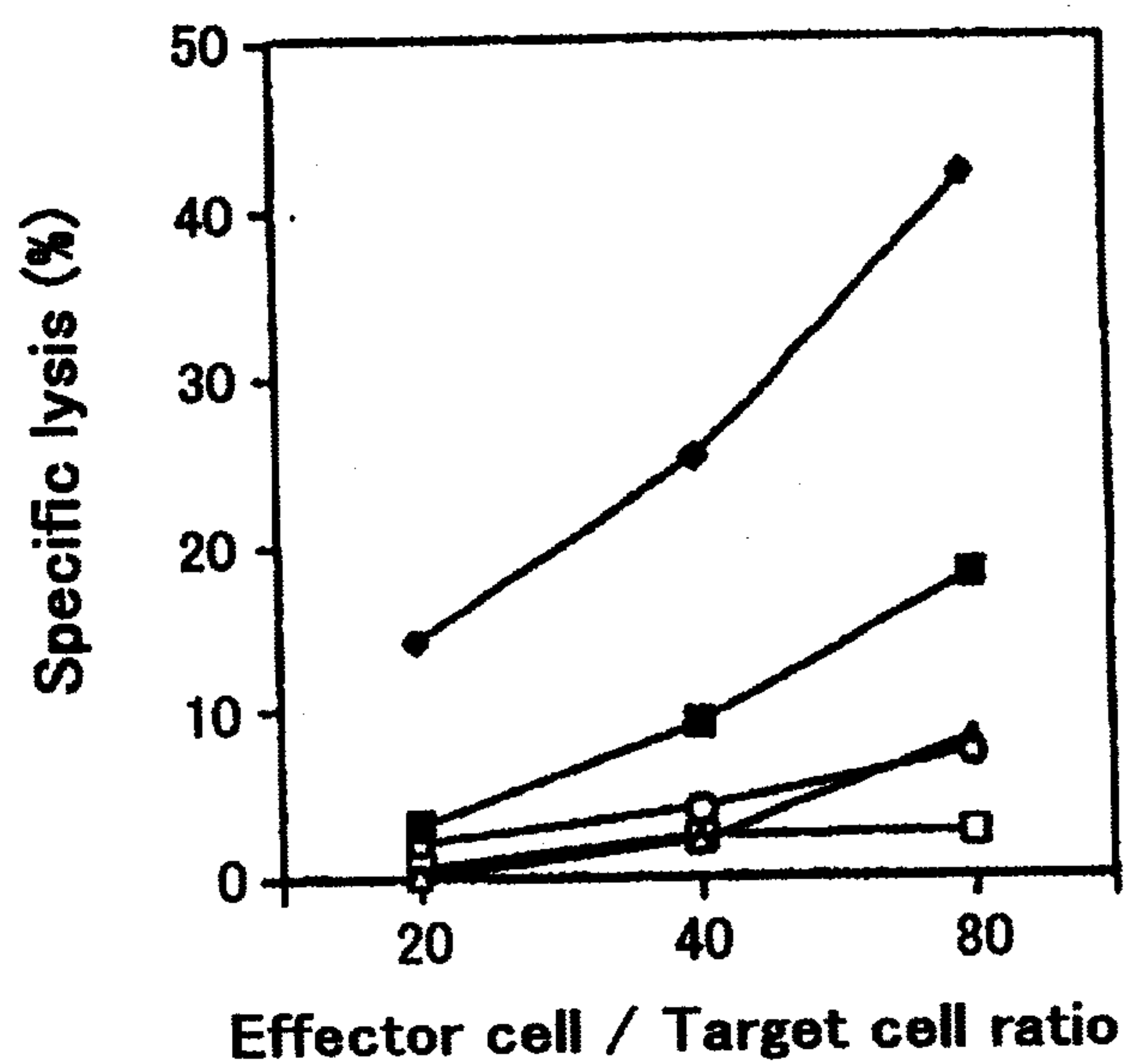
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Figure 12

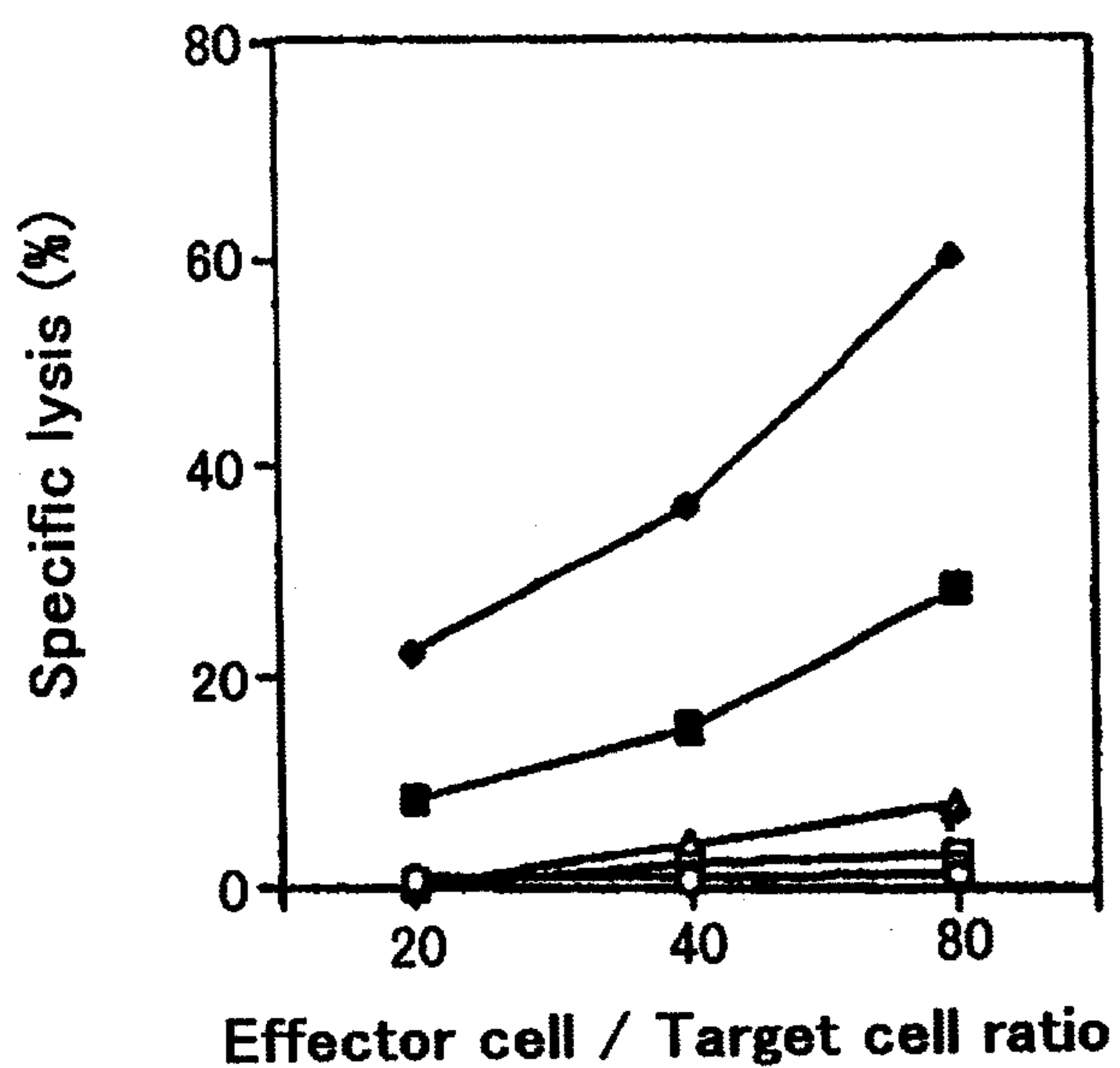
(A) P1
(UBE2V 43-51)



(B) P3
(UBE2V 85-93)



(C) P5
(UBE2V 208-216)



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Figure 13

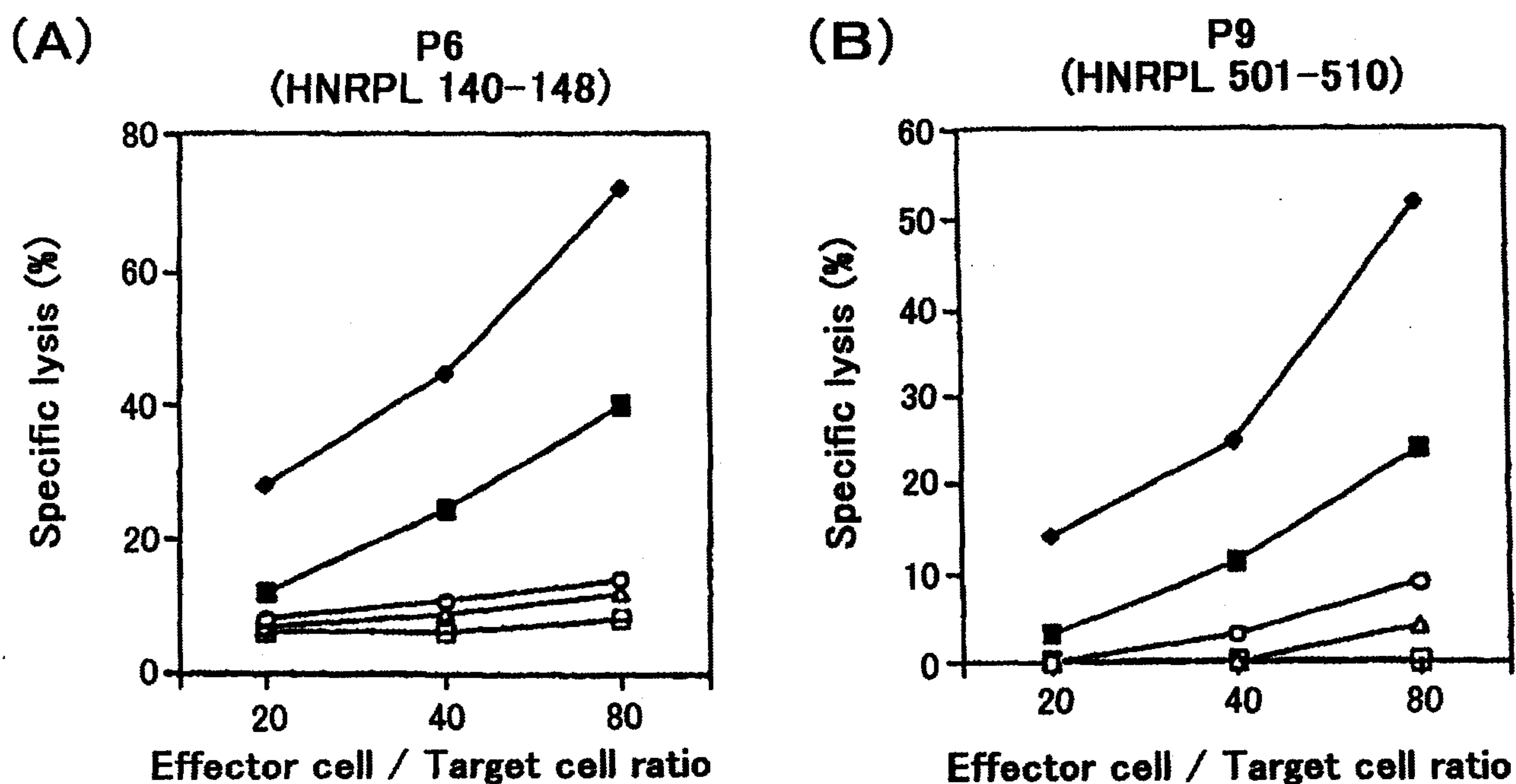


Figure 14

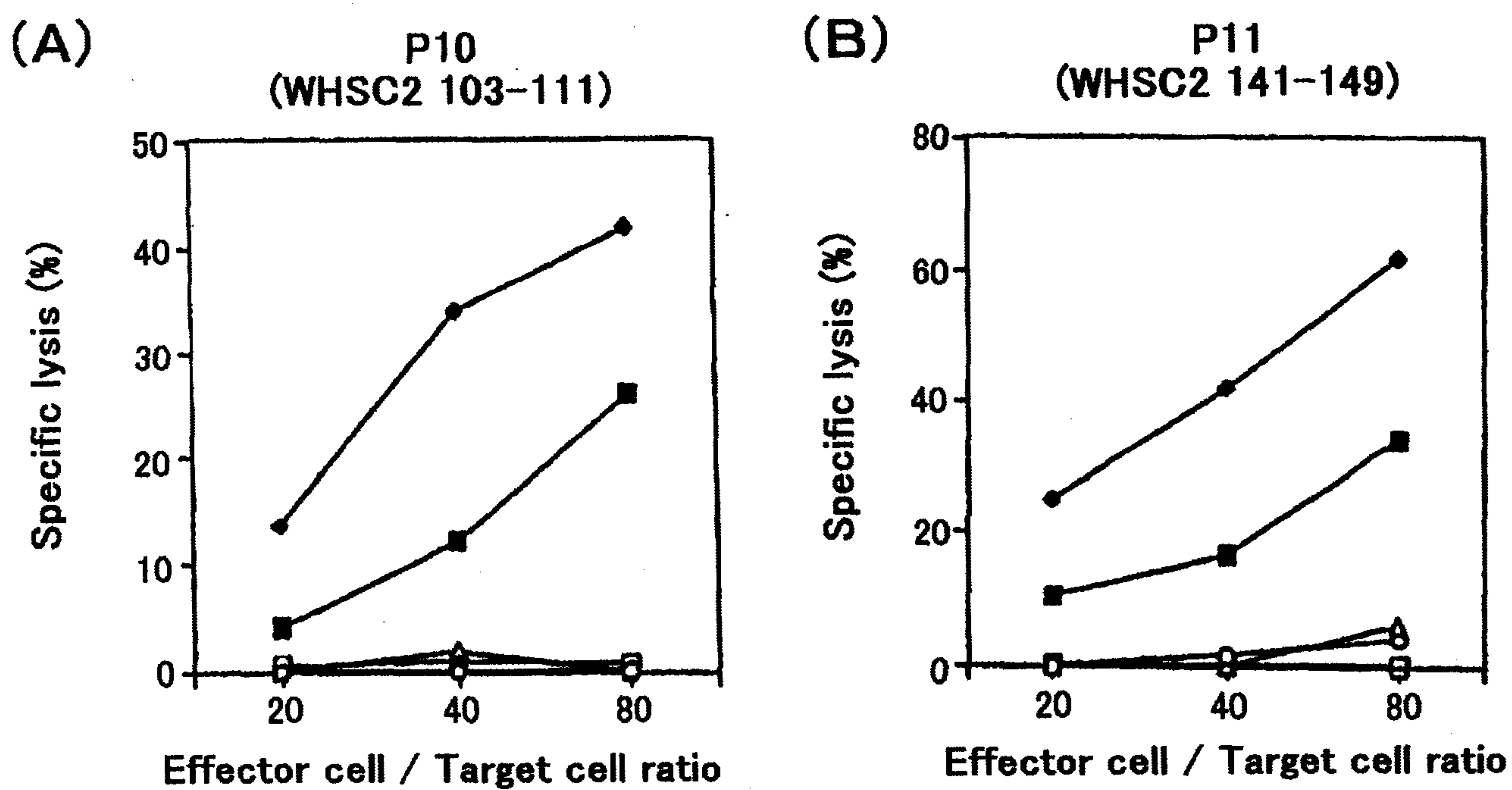


Figure 15

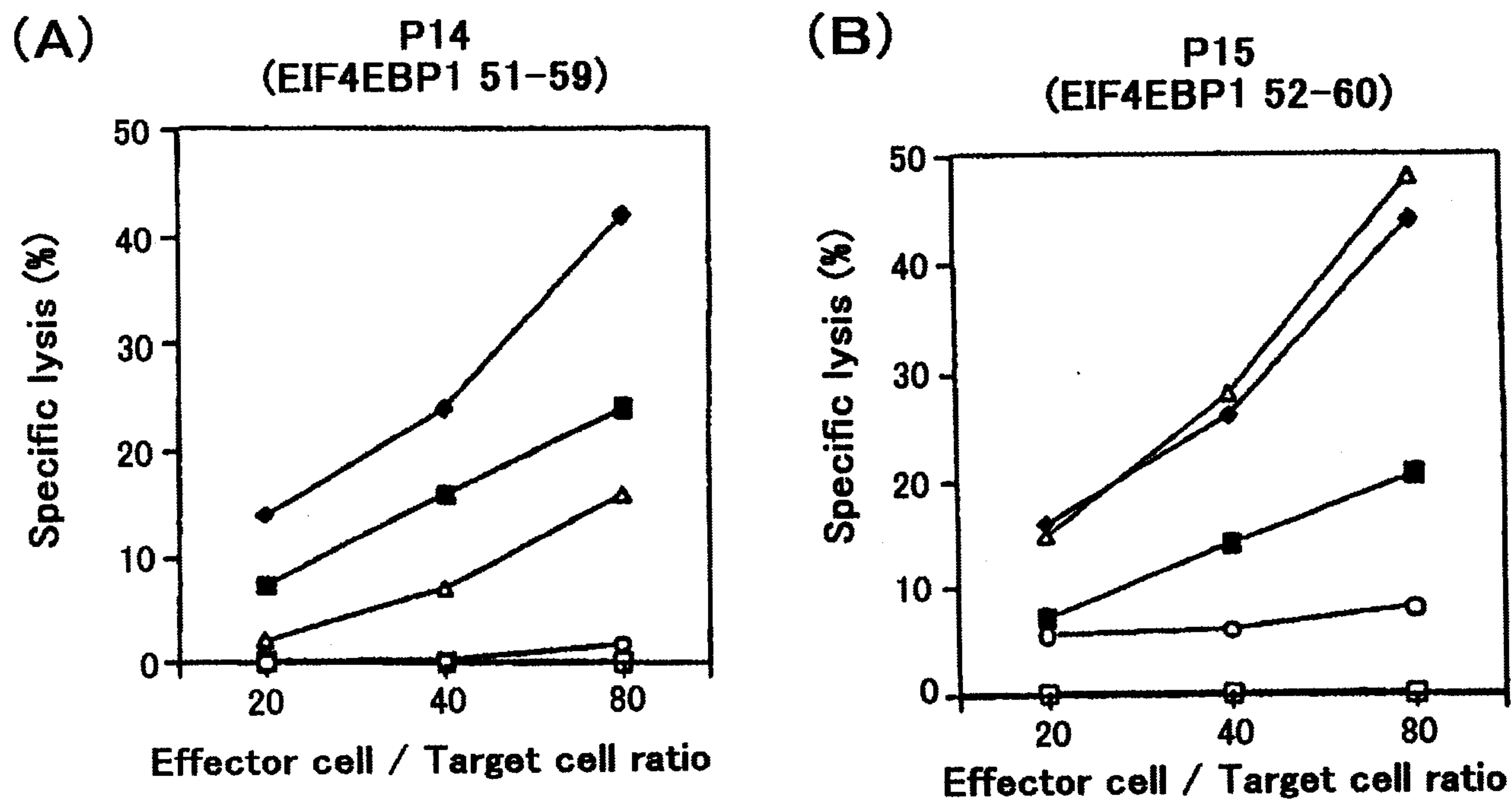
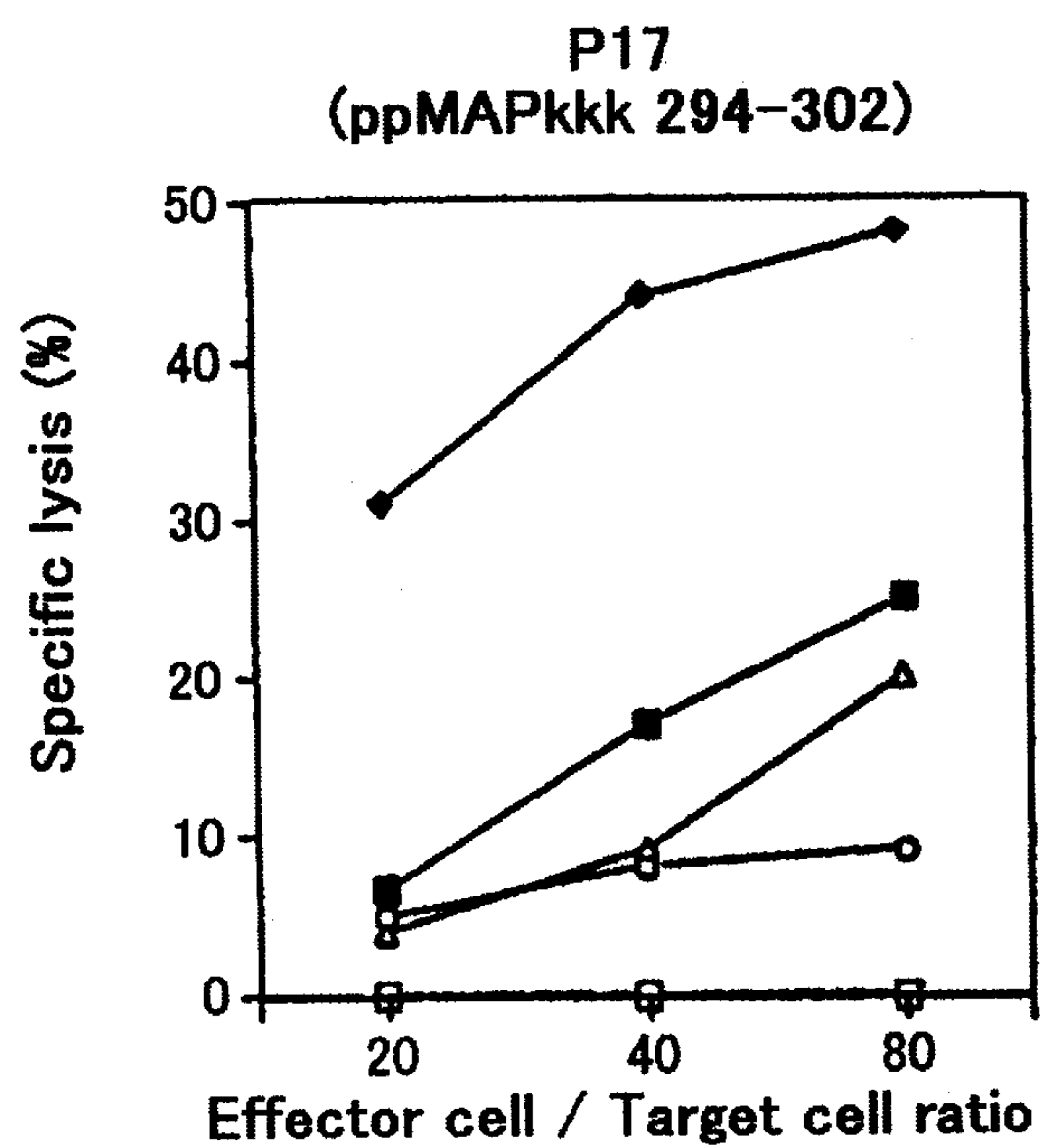


Figure 16



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Figure 17

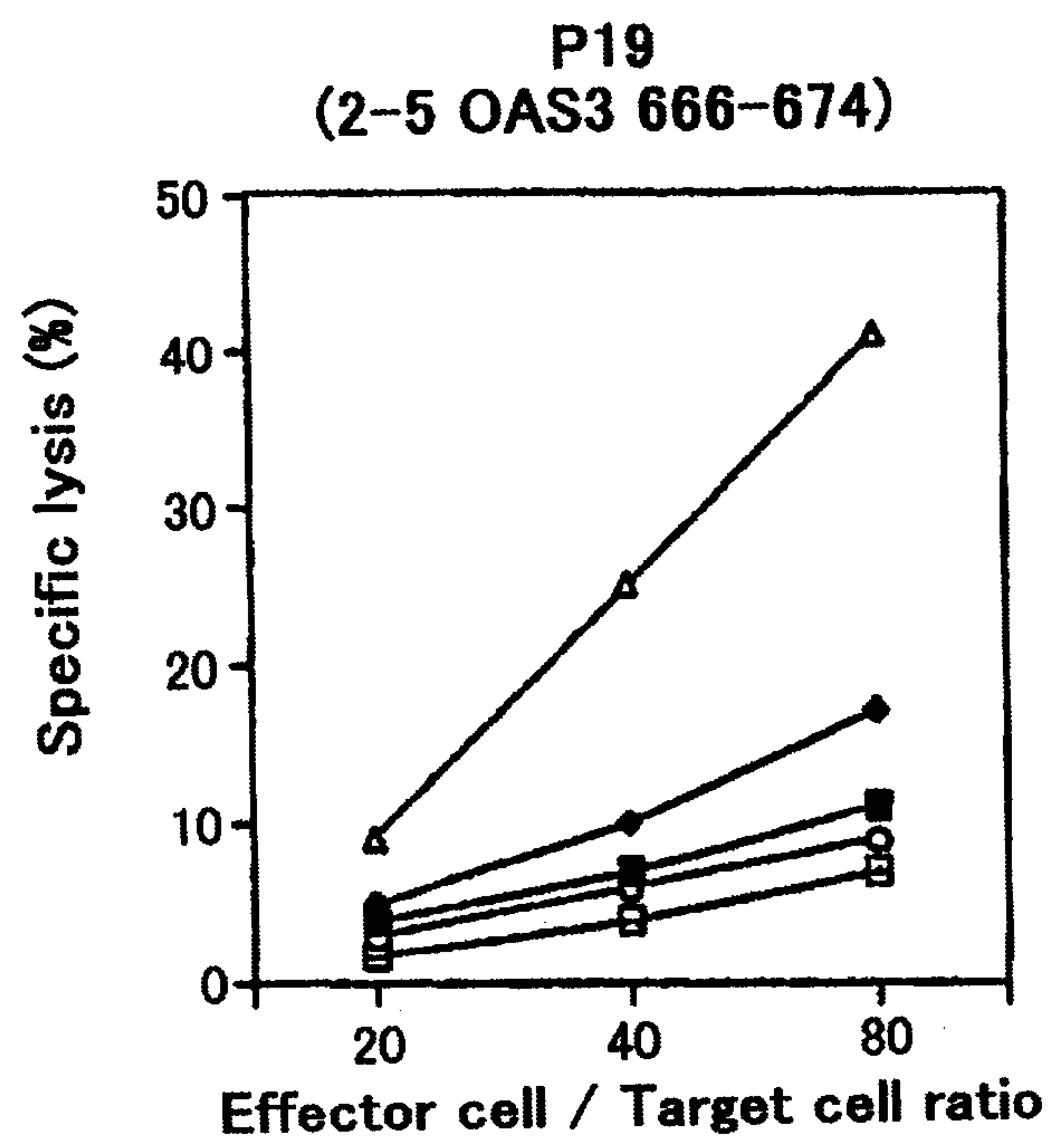


Figure 18

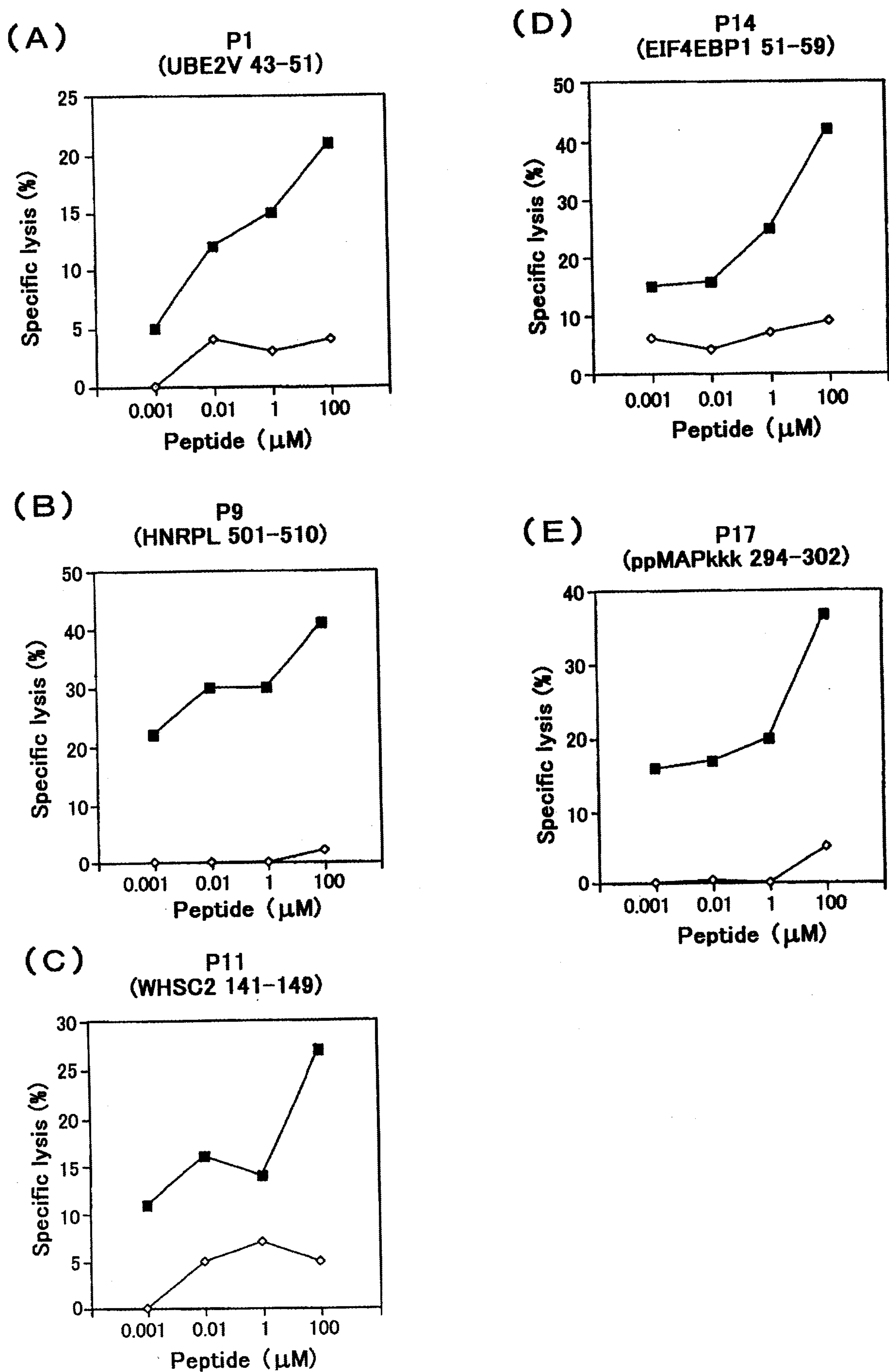
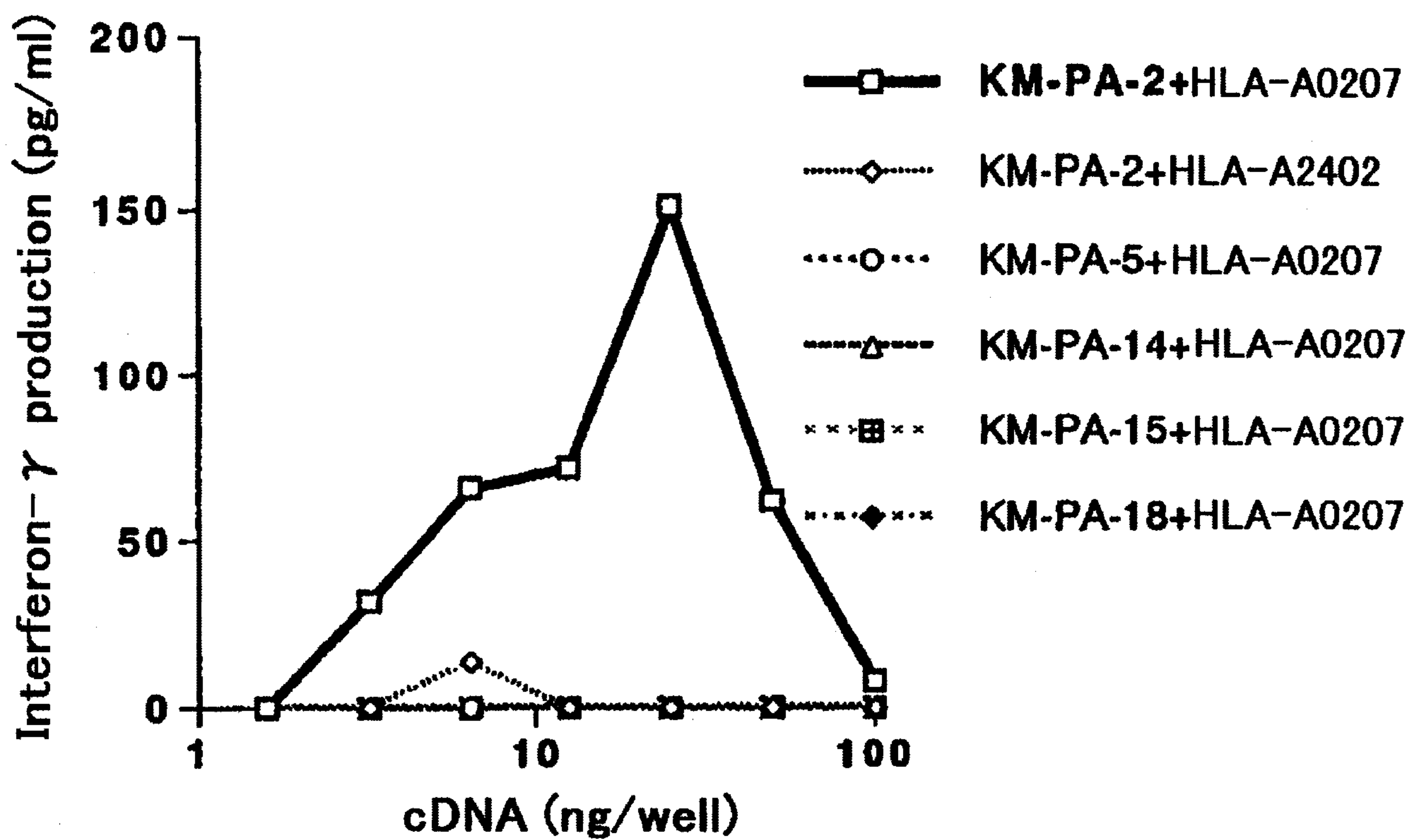
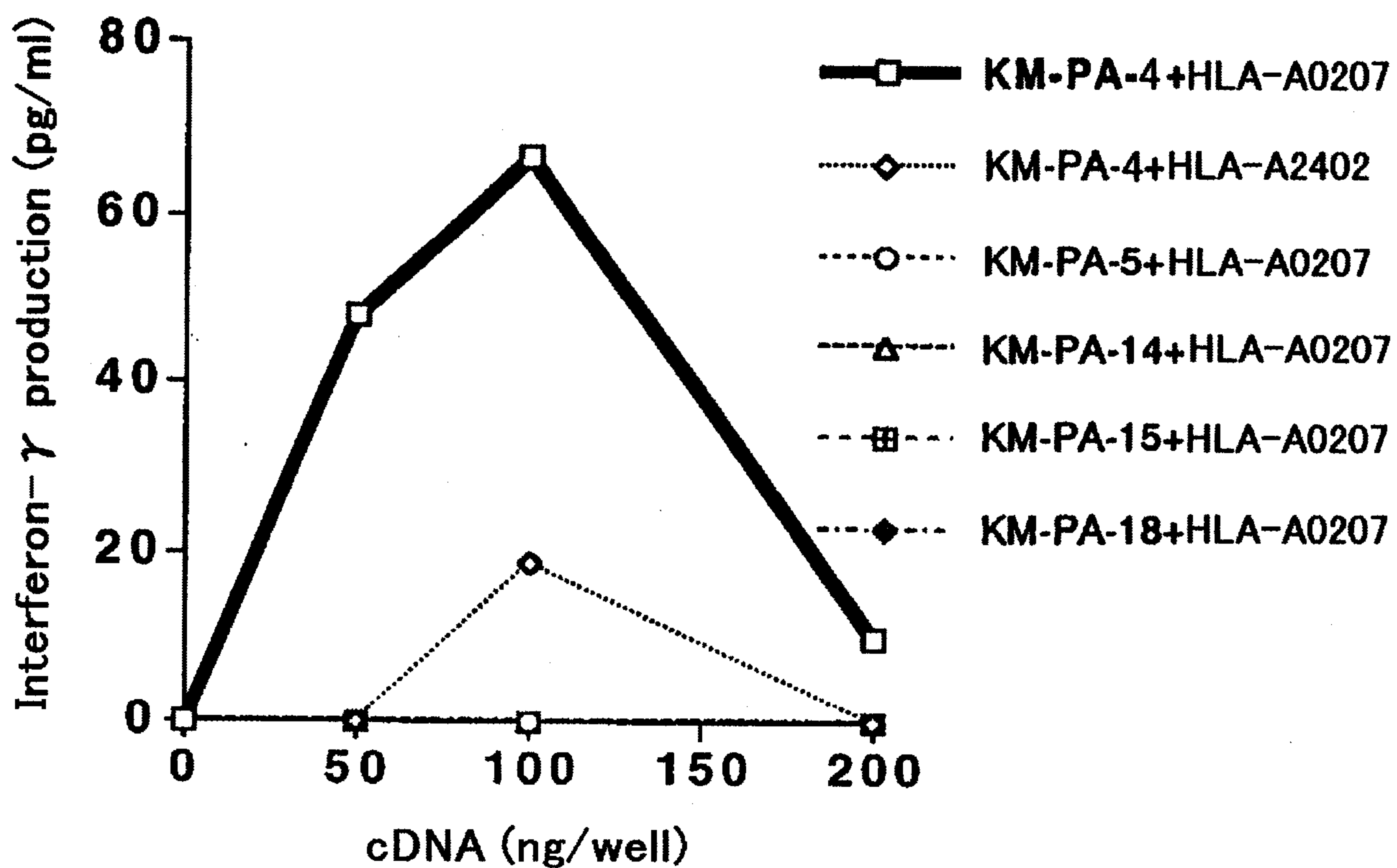


Figure 19

(A)



(B)



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Figure 20

