

CHIMERIC ANTIGEN RECEPTOR, AND T CELLS IN WHICH CHIMERIC

ANTIGEN RECEPTOR IS EXPRESSED

TECHNICAL FIELD

5 The present invention relates to a chimeric antigen receptor recognizing a cancer cell surface antigen, and a T cell in which the receptor is expressed. Specifically, the present invention relates to a chimeric antigen receptor with an excellent expression rate, and a T cell in which the receptor is expressed. More specifically, the present invention relates to a chimeric antigen receptor and a T cell in which the receptor is expressed, said chimeric antigen receptor comprising a cancer cell surface antigen binding domain; a hinge region; a
10 transmembrane domain; a costimulatory domain; and a cytoplasmic signaling domain, characterized in that the costimulatory domain consists of mutated CD28 or TNFRSF9. Additionally, the present invention relates to a chimeric antigen receptor and a T cell in which the receptor is expressed, characterized in that the antigen binding domain binds to an antigen
15 selected from the group consisting of IL13R α 2, an antigen associated with an angiogenic activity, EGFRvIII, EphA2, α V β 3, and glypican1.

In addition, the present invention relates to the chimeric antigen receptor and the T cell in which the receptor is expressed, characterized in that three glycines are additionally
20 introduced between the antigen binding domain and the hinge region.

Further, the present invention relates to the chimeric antigen receptor and the T cell in which the receptor is expressed, characterized in that the cytoplasmic signaling domain uses a CD3 ζ signaling domain of a normal person where extra Glutamine is comprised, not a CD3 ζ signaling domain of a Jurkat T cell.

Moreover, the present invention relates to the chimeric antigen receptor and the T cell in which the receptor is expressed, the chimeric antigen receptor comprising any one of the predetermined antigen binding domain, the costimulatory domain and the cytoplasmic signaling domain described above, or all of them.

BACKGROUND FIELD

T cells (hereinafter, in the present specification, this is sometimes referred to as “CAR-T cells”) expressing chimeric antigen receptors (hereinafter, in the present specification, this is sometimes referred to as “CARs”) mean recombinant T cells in which a gene coding a receptor recognizing a cancer cell surface antigen specifically expressed on the surface of the cancer cell is introduced into the T cell to kill the cancer cell. Dr, Zelig Fshhar, *et. al.*, who is a chemist and an immunologist of the Weizmann Institute of Science in Israel, had succeeded in making T cells provided with chimeric antigen receptors, by obtaining a theory that when T cells with a receptor binding to an antigen specifically expressed in a cancer cell is artificially

made, an immune response occurs, targeting only to the cancer cell, so as to kill the cancer cell, and then reported this fact in PNAS in 1989.

However, CAR-T cells produced in the early stage, i.e. the 1st generation CAR-T cells used only CD3 ζ as a signaling domain, but its therapeutic effect was insignificant, and also, there was a disadvantage that the duration time was short. Thus, efforts have been made to improve the reactivity of the CAR-T cells, and as a result, 2nd generation CAR-T cells in which a costimulatory domain (CD28 or CD137/4-1BB) and CD3 ζ are combined were produced, wherein the number of CAR-T cells present in the body was significantly increased as compared to the number of the 1st generation CAR-T cells. Meanwhile, the 2nd CAR-T cells used one type of the costimulatory domain, and CAR-T cells using two types of the costimulatory domain are referred to 3rd generation CAR-Ts. Most of the recent studies focus on the 2nd generation and 3rd generation CAR-T cells. Meanwhile, regarding methods for treating cancers using the CAR-T cells, there was a report that when cytotoxic T cells transformed to recognize CD19 were injected into three patients with end-stage chronic lymphoid leukemia (CCL), leukemia was completely treated in two of the patients, and the condition was continued for about 10 months (N. Engl J Med 2011; 365:725-733 August 25, 2011, Sic. Transl. Med 2011 Aug 10;3(95):95ra73). The CAR-Ts used herein correspond to the 2nd generation, and use 4-1BB as the costimulatory domain and CD3 ζ as the signaling domain. The antigen binding domain of the CAR-T cells recognizes CD19, which is found

on the surface of the leukemia cancer cells, as an antigen.

In addition, there was a report that when patients with acute leukemia were treated by administering CTL019, 27 of the 30 patients had experienced complete remission, 67% of all patients experienced complete remission for 2 years, and 78% of the patients were survived for 2 years. Given that the subject patients were relapsing or refractory patients, this result was very surprising (N Engl J Med 2014; 371:1507-1517, October 16, 2014).

At present, for therapeutic methods using various CAR-T cells, clinical tests on various hematologic cancers such as lymphoma, myeloma, etc. have been conducted, and it is expected that CAR-T will become available as an available medicine in the market. Since cancer treatment using CAR-T cells is a self-derived method, this product could not be mass-produced; however, this is patient-specific treatment, so its therapeutic effect is incomparably higher than the existing anticancer drugs.

[Patent Literature]

Korean Patent Laid-Open No. 10-2013-0124521

[Non-Patent Literature]

Immunol Rev, 2014, 257(1):107-126

N Engl J Med 2014; 371: 1507-1517, October 16, 2014

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DETAILED DESCRIPTION OF INVENTION

5 SUMMARY OF INVENTION

The present invention has a task for providing CAR and CAR-T cells with significantly excellent expression rates and therapeutic effects as compared to the conventionally known CAR-T cells. More specifically, the present invention has a task for providing, in the 2nd generation and 3rd generation CAR-T cells, a costimulatory domain
10 capable of being introduced into various CAR-T cells, as the costimulatory domain serving a main role in the function. Furthermore, the present invention has a task for providing various antigen binding domains capable of binding to an antigen expressed on the surface of a specific cancer cell and also capable of forming CAR-T cells. In addition, the present invention has a task for providing a method for improving the expression rates of various
15 CAR-T cells and the therapeutic effects thereof, with a chimeric antigen receptor characterized by having further amino acid sequences that can be additionally introduced between the antigen binding domain and the hinge domain.

MEANS FOR ACHIEVING TASK

20 As means for achieving the aforementioned tasks, the present invention describes the

following technical idea.

Disclosed is a chimeric antigen receptor and a CAR-T cell in which the receptor is expressed, the chimeric antigen receptor comprising an antigen binding domain; a hinge region; a transmembrane domain; a costimulatory domain; and a cytoplasmic signaling domain, characterized by independent comprising a specific costimulatory domain, or a specific antigen binding domain, and a specific amino acid sequence added between the antigen binding domain and the hinge domain, or in that the cytoplasmic signaling domain uses a CD3 ζ signaling domain of a normal person where extra Glutamine is comprised, not a CD3 ζ signaling domain of a Jurkat T cell, or by comprising a combination thereof.

EFFECT OF INVENTION

The CAR-T cell comprising the antigen binding domain; or the costimulatory domain; or the signaling domain described in the present invention has the effect that the therapeutic efficacy and expression rate are significantly excellent.

BRIEF DESCRIPTION OF DRAWINGS

The current embodiments are illustrated in the drawings for the purpose of exemplifying the present invention. However, it should be noted that the present invention is not limited to the accurate arrangements and methods of the embodiments illustrated in the

drawings.

Figure 1 illustrates a retrovirus vector and transgene representing the main functional elements of one embodiment of the CAR-T cell described in the present invention.

5 Specifically, this figure illustrates a clinical-grade retrovirus vector indicating the expressions of mutated IL13(E11K.R64D.S67D.R107K), human CD8 α hinge and human CD8/human CD3 transmembrane domain in order to impart higher antigen affinity than two amino acid substituents (Glu-11, Arg-107) of IL13, and mutant human CD28(RLLH→RGGH), human TNFRSF9, and CD3 zeta signaling domain of healthy person in order to increase the CAR
10 expression rate. This figure is not illustrated in a constant accumulation.

Figure 2 shows that the expression rate is increased after adding three glycines between the antigen binding domain and the hinge region, in order to increase the solubility of a CAR protein so as to increase the expression of the chimeric antigen receptor.

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Figure 3 shows that the expression rate is increased when using mutant (RLLH→RGGH) of human CD28, in order to increase the expression of the chimeric antigen receptor of the CAR protein.

20 Figure 4 shows the result of analyzing transformed T cell using a Flow cytometry

analysis, in order to verify the purity of CAR-T cell and the expression rate of CAR produced by a production process set for clinical test. This figure shows the CAR expression rate and the T cell purity.

5 Figure 5 shows the comparison of cytotoxicity of T-cells, in which IL13 (Glu-11, Arg-107) where two positions are substituted, and IL13(IL13.E11K.R64D.S67D.R107K) where four positions are substituted are introduced.

Figure 6 shows CAR repression rate-dependent anticancer activity increase in human
10 brain cancer cell line U251 of CAR-T cells consisting of
IL13(E11K.R64D.S67D.R107K).TNFRSF9. CD3 ζ where four positions are substituted.

Figure 7 shows IFN- γ cytokine production after culturing human brain cancer cell line U251 (IL13R α 2 overexpression), which is a target cell with CAR-T cells consisting of
15 IL13(E11K.R64D.S67D.R107K).TNFRSF9.CD3 ζ where four positions are substituted or HUVEC (lack of IL13R α 2 expression) which is a normal cell control, at a ratio of 0.5 : 1 for 19 hours.

Figure 8 shows that a dose-dependent (CAR+T-cell number) *increase* in IFN- γ
20 cytokine secretion, after culturing human brain cancer cell line U251, which is a target cell

with CAR-T cells comprising (IL13.E11K.R64D.S67D.R107K).TNFRSF9.CD3 ζ where four positions are substituted.

Figure 9A is an image briefly showing the nude mouse *in vivo* efficacy experiment method using the CAR-T cells comprising IL13(E11K.R64D.S67D.R107K)TNFRSF9.CD3 ζ where four positions are substituted; and Figure 9B shows the result of measuring the tumor size of the animal 12 days after the treatment with the CAR-T cell or PBS.

Figure 9C shows the shape, size and weight of the cancer tissue removed from the nude mouse 15 days after the treatment with the CAR-T cell or PBS.

Figure 10A is an image for the removed cancer tissues stained with anti-human CD3 antibody in order to stain human CAR-T or T cell, from the nude mouse 15 days after the treatment with TMZ+PBS (PBS was intravenously administered once, and TMZ and IL-2 were intraperitoneally and intravenously administered once a day for four days).

Figure 10B is an image for the removed cancer tissues stained with anti-human CD3 antibody in order to stain human CAR-T or T cell, from the nude mouse 15 days after the treatment with TMZ+YYB103 (TMZ and CAR-T cell comprising IL13(E11K.R64D.S67D.R107K)TNFRSF9.CD3 ζ where four positions are substituted were

intravenously administered once, and TMZ and IL-2 were intraperitoneally and intravenously administered once a day for four days).

Figure 11A is an image for the removed cancer tissues stained with H&E from the nude mouse 15 days after the treatment with TMZ+PBS (PBS was intravenously administered once, and TMZ and IL-2 were intraperitoneally and intravenously administered once a day for four days).

Figure 11B is an image for the removed cancer tissues stained with H&E from the nude mouse 15 days after the treatment with TMZ+YYB103 (TMZ and CAR-T cell comprising IL13(E11K.R64D.S67D.R107K)TNFRSF9.CD3 ζ where four positions are substituted were intravenously administered once, and TMZ and IL-2 were intraperitoneally and intravenously administered once a day for four days).

Figure 12 shows the production of anti-angiogenic CAR. Successful anti-cancer CAR therapies require not only antigen-specific CAR-T cells but also accessing CAR-T cells to cancer cells and maintaining CAR-T cell function in the immunosuppressive tumor microenvironment. Therefore, anti-angiogenic CAR was produced. Figure 12A illustrates the retrovirus vector and transgene representing the main functional element of Anti-Angiogenic CAR; Figure 12B shows the result of analyzing transformed cells checking on the cell surface

expression of Anti-Angiogenic CAR using a Flow cytometry analysis.

Figures 13 to 16 show the four kinds of CAR production, targeting a major tumor antigen of various cancers. A of the respective figures illustrates the retrovirus vector and transgene representing the main functional element; B of the respective figures shows the result of analyzing transformed cells checking on the cell surface expression of Anti-Angiogenic CAR using a Flow cytometry analysis.

BEST MODE FOR EMBODIMENT OF INVENTION

The CAR-T cell according to the present invention is a recombinant T cell in which a receptor gene recognizing a cancer cell as an antigen is introduced, wherein the T cell consists of an antigen binding domain recognizing the antigen; a hinge region (or spacer) connecting the antigen binding domain and a transmembrane domain; the transmembrane domain; a costimulatory domain; and a cytoplasmic signaling domain.

The antigen binding domain, which is a site where a main signal is delivered and is present outside of a cell membrane, recognizes a cancer cell expressing a particular antigen. Thus, in the cancer treatment using CAR-T cell, the detailed treatment subject is determined by the antigen binding domain. The present invention describes, for example, a chimeric antigen receptor capable of specifically binding to IL13Ra2 overexpressed in glioblastoma,

but the antigen binding domain is not specifically limited thereto. Glioblastoma (GMB) or glioblastoma multiforme is one of the most general brain tumors, which occupies about 12 to 15% of the brain tumors, and this is a general malignant brain cancer. Since this cancer is relatively rare as compared to a colorectal cancer or lung cancer, the studies on the treatment method thereof have not been actively conducted. The cells of glioblastoma are similar to astrocyte, but astrocyte serves as maintaining nerve cells and giving nutrition to nerves and a defense reaction to the damage of brain tissues. It is believed that genomic abnormality of stem cells or immature astrocyte is involved in occurrence and malignization of glioblastoma. For the treatment of glioblastoma, surgery, radiotherapy and chemotherapy are used. As chemotherapy, temozolomide, lomustine and carmustine, etc. are used, and recently, clinical tests such as tumor vaccine treatment and molecular targeted treatment have been conducted. However, there are still no useful therapeutic agents for the treatment of glioblastoma, and particular, although there was an attempt on the treatment of glioblastoma overexpressing IL13R α 2 using CAR-T cells using mutant IL13 where the 11th position is substituted with E11Y, Baylor college of medicine group reported that the therapeutic effect using the CAR-T cells using mutant IL13 where the 11th position is substituted with E11Y was not good *in vivo*. However, the CAR-T cell described in the present invention exhibits the excellent therapeutic effect of glioblastoma.

Sequence of the antigen binding domain binding to IL13R α 2 is identical to SEQ ID

NO. 1, and in particular, mutant IL13 where the 11th, 64th, 67th and 107th positions are substituted with E11K.R64D.S67D.R107K, respectively, is newly described in the present invention. It should be noted, however, that the amino acids substituted in the corresponding positions can be replaced with amino acids having the similar property with the specific amino acids. Thus, the amino acids can be replaced with arginine (R) or histidine (H), instead of lysine (K), in the 11th position; with glutamic acid (E), instead of aspartic acid (D), in the 64th and 67th positions; and histidine (H), instead of lysine (K), in the 107th position.

IL13(E11K.R64D.S67D.R107K) where the four positions are mutated, described in the present invention, and analogue substituted with an amino acid having the same property in the same position have improved antigen affinity.

The antigen binding domain of the present invention can be produced so as to bind to an antigen expressed in various cancer cells as well as IL13R α 2 overexpressed in glioblastoma. For example, an antigen binding domain (SEQ ID NO. 2) capable of binding to an antigen associated with an angiogenic activity; an antigen binding domain (SEQ ID NO. 3) binding to EGFRvIII which is a main tumor antigen of glioblastoma and lung cancer, etc.; an antigen binding domain (SEQ ID NO. 4) binding to EphA2 which is a tumor antigen of glioblastoma, breast cancer, prostate cancer, etc.; an antigen binding domain (SEQ ID NO. 5) binding to α V β 3 which is a resistant marker of carcinoma stemness and receptor tyrosine kinase

inhibitors (RTKIs) such as erlotinib of pancreatic cancer, lung cancer and breast cancer; an antigen binding domain (SEQ ID NO. 6) binding to glypican1 overexpressed in pancreatic cancer, glioblastoma, breast cancer, etc. are described in the present invention. Figures 12 to 16 show the five kinds of CAR production comprising the above antigen binding domains. The respective figures illustrates the retrovirus vector and transgene representing the main functional element and shows the result of analyzing transformed cells checking on the cell surface expression of Anti-Angiogenic CAR using a Flow cytometry analysis.

The further characteristic of the present invention lies in additionally introducing three glycines between the antigen binding domain and the hinge region, in order to increase the solubility of a CAR protein to increase the expression of the chimeric antigen receptor. According to the study of the present inventors, the difference in solubility between the receptor in which three glycine between the antigen binding domain and the hinge region are introduced and the receptor in which three glycine are not introduced showed about 10 times, and this difference leads to a great difference in expression rate with regard to the production of CAR-T cells, and the difference of the expression rate is eventually directly connected to the therapeutic effect. For this reason, this can be deemed to be very advanced technical development. In addition, said three glycine (G) may be substituted with alanine(A), valine(V), leucine(L) or isoleucine(I), which are amino acids having the similar property.

Yet another characteristic of the present invention lies in the use of a specific costimulatory domain. In the CAR-T cells, when an antigen binding domain and an antigen bind to each other, the signal activates a T cell immune response through the cytoplasmic signaling domain (CD3 ζ). The costimulatory domain, which is a site where a costimulatory signal is delivered, serves a role in delivering a signal such that the CAR-T cell recognizing a specific antigen binding to the antigen binding domain causes an immune response to help proliferation and persistence in the body longer. Meanwhile, such costimulatory domain is a component which was not present in the first generation CAR-T cell, and the 2nd CAR-T cell uses one costimulatory domain, and the 3rd generation CAR-T cell uses two costimulatory domains. The CAR-T cell improves proliferation and persistence in the body longer. in the costimulatory domain inside the cells over the generations such as 1st generation, 2nd generation, 3rd generation, etc., and thus the cells have been developed in re-combination with genes such that many CAR-T cells against the cancer cell are made in the body even after injecting a small number of cells, and the cells can last in the body for a long time even after injection. That is, in the case of the first generation, there was a limitation of signaling because it comprises only CD3 ζ without the costimulatory domain, but in the 2nd and 3rd generations, 4-1BB or OX40, etc. is additionally introduced so as to improve proliferation and persistence in the body longer.

In addition, the present inventors used the costimulatory domain which generates a

mutant in the predetermined position of CD28 such that by the improvement of the expression rate of CAR-T cells, the therapeutic effect can be exhibited even if less CAR-T cells are used, and furthermore, the inventors have found that by using two costimulatory domains in which mutated CD28 and TNFRSF9 are combined, 'proliferation and persistence in the body' is improved, resulting in the increased therapeutic efficacy.

Accordingly, the further technical characteristic of the present invention lies in a chimeric antigen receptor and a CAR-T cell in which the receptor is expressed, the chimeric antigen receptor consisting of an antigen binding domain; a transmembrane domain; a costimulatory domain and a cytoplasmic signaling domain, wherein the costimulatory domain comprises CD28 or TNFRSF9, or CD28 and TNFRSF9. Here, CD28 may comprise a mutant (Sequence Nos. 6 to 9 are substituted from RLLH to RGGH) for increasing the expression of the chimeric antigen receptor. Amino acid sequences of the wild type of CD28 and TNFRSF9, which may be comprised as the costimulatory domain of the present invention, are indicated with Sequence Nos. 7 and 8. In addition, in the mutated CD28 (Sequence Nos. 6 to 9 are substituted from RLLH to RGGH), the substituted amino acid is glycine(G), but this can be replaced with amino acid similar thereto, for example alanine(A), valine(V), leucine(L) or isoleucine(I). The hinge region of the present invention is a portion connecting the antigen binding domain and the transmembrane domain, and this is also called spacer. The hinge region has the purpose for expanding the antigen binding domain from T cell membrane. As

the hinge region of the present invention, a hinge region typically used in the pertinent technical field can be used, and for example, the hinge region can be derived from CD8 hinge region (SEQ ID NO. 9, SEQ ID NO. 10). As aforementioned, another technical characteristic of the present invention lies in three glycines additionally introduced between
5 the antigen binding domain and the hinge region.

The transmembrane domain of the present invention serves a role as an anker of CAR molecular and at the same time a role in delivering a signal received from the antigen binding domain to the costimulatory domain and the cytoplasmic signaling domain. The
10 transmembrane domain is not limited to the transmembrane domain of the present invention, and typical transmembrane domains used for the CAR production can be used, and for example, human CD8/CD3 transmembrane domain can be used (SEQ ID NO. 11, SEQ ID NO. 12).

15 As the cytoplasmic signaling domain of the present invention, a CD3 ζ signaling domain of a normal person where extra Glutamine is comprised, not a CD3 ζ signaling domain of a Jurkat T cell, was used, and the extra glutamine means glutamine(Q) in the 50th position in SEQ ID NO. 13.

20 The technical idea of the present invention includes both the use of the

aforementioned technical characteristics alone and the use of the combination thereof. That is, the implementation of the technical characteristics of the present invention includes all of the CAR-T cells comprising the predetermined antigen binding site described in the present invention; the CAR-T cells in which three glycine are additionally introduced between the antigen binding domain and the hinge region; and the CAR-T cells comprising the costimulatory domain described in the present invention.

The nucleic acid sequences of polypeptide constituting the domains described in the present specification can be obtained using the recombinant methods known in the pertinent technical field, and for example, can be obtained by screening library from cells expressing the gene using the standard technique, or inducing a gene from a known vector to comprise the same gene, or directly isolating from cells or tissues comprising the same gene. Alternatively, the interested gene can be generated by synthesis, not cloning.

The method for introducing and expressing a gene into cells has been known in the pertinent technical field. The expression vector can be rapidly introduced into host cells by any method known in the pertinent technical field. For example, in the present invention, the CAR-T cells can be produced by joining a CAR gene fragment finally produced to an MFG retrovirus expression vector cleaved with XhoI/NotI. It should be understood that the present invention comprises any various mutants for each of the components of the structure.

Cancers to be treated may include non-solid tumors (for example, hematological tumors, e.g. leukemia and lymphoma) as well as glioblastoma, or may include solid tumors.

5 As such, it takes several steps to produce recombinant CAR-T cells and inject the cells into cancer patients. T cells are isolated from the blood of patients, and then DNA designed with CAR is introduced into the T cells using an expression vector, and the CAR-T cells are proliferated, and then injected back into the patient.

10 **MODE FOR CARRYING OUT THE INVENTION**

Hereinafter, the present invention is specified through the examples. Please be noted, however, that the following examples are not intended to limit the technical scope of the present invention in any meaning.

15 Example 1: Construction of an expression vector having 2nd generation (YYB-103, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ) and 3rd generation (YYB-103A, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ) chimeric antigen receptors specifically binding to IL13R α 2 overexpressed in cancer cell

The present inventor produced mutant IL13(E11K.R64D.S67D.R107K) in order to
20 impart a higher antigen affinity than two amino acid substitutions (Glu-11, Arg-107) of IL13,

and produced chimeric antigen receptors comprising one co-stimulation domain (TNFRSF9) and two co-stimulation domains (CD28, TNFRSF9) of the cytoplasmic signaling domain of CAR-T cell (Figure 1). In the present invention, three glycines were added between the antigen binding domain and the hinge region in order to increase the solubility of a CAR protein to increase the expression of the chimeric antigen receptor (Figure 2). The CD28 cytoplasmic signaling domain used in the present invention comprises mutant (RLLH→RGGH) human CD28 DNA sequences for increasing the solubility of a CAR protein to increase the expression of the chimeric antigen receptor (Figure 3). Human CD3ζ signaling domain of healthy normal person, not a CD3ζ signaling domain of a Jurkat T cell, was used. Human IL13(P35225.1), human CD3(P20963-1), human CD8α(P01732), human CD28(P10747), human TNFRSF9(Q07011), and human kappa light chain signal sequence (HuVHCAMP) were optimized using science literatures and publicly available database, the 2nd and 3rd generation chimeric antigen receptors (YYB-103, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3ζ and YYB-103A, IL13.E11K.R64D.S67D.R107K.28.TNFRSF9.CD3ζ) consisting of codon-optimized synthetic DNA was produced (Figure 1). The completed structure comprises kozak consensus ribosome-binding sequence, human kappa light chain signal sequence (HuVHCAMP), human IL13.E11K.R64D.S67D.R107K mature protein sequence (human IL13(E11K.R64D.S67D.R107K)), an addition of three glycine (GGG) between the antigen binding domain and the hinge region in order to increase the solubility of a CAR protein to

increase the expression of the chimeric antigen receptor (Figure 2), the hinge region of human CD8 α , human CD8/CD3 transmembrane domain, the costimulatory domain of cytosol CD28 transformed to mutant (RLLH→RGGH), the costimulatory domain of cytosol TNFRSF9, CD3 ζ cytoplasmic signaling domain of healthy person and XhoI/NotI cleavage portion. The entire sequences of YYB-103 and YYB-103A are represented in Sequence Nos. 14 and 15. A CAR gene fragment finally produced was joined to an MFG retrovirus expression vector cleaved with XhoI/NotI (Emtage PC, etc., Clin Cancer Res, 2008 14L8112-8122) (Figure 1). In the present example, in order to compare the activity of chimeric antigen receptors, two amino acid substitutions (Glu-11, Arg-107), 3rd generation chimeric antigen receptors (YYB-103B, IL13(E11K.R107K).28.TNFRSF9.CD3 ζ) of IL13 was additionally produced (SEQ ID NO. 16).

Example 2: Production of T cells transformed to 2nd generation (YYB-103, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ) and 3rd generation (YYB-103A, IL13.E11K.R64D.S67D.R107K.28.TNFRSF9.CD3 ζ) chimeric antigen receptors specifically binding to IL13R α 2 overexpressed in cancer cells.

PG13 clone with high titer, expressing CAR, was produced by temporarily infecting phoenix-empo and phoenix-eco cells with the retrovirus expression vector YYB-103 or YYB-103A produced in Example 1, and subsequently transduced PG13 cells with acellular vector

stock from the infected phoenix-empo and phoenix-eco cells. Single clone with high titer was obtained by a flow cytometer after staining PG13/YYB-103 cells using an anti-IL-13 monoclonal antibody (BD Pharmingen). PG13/YYB-103 single clone with high titer was produced by the second subcloning according to the limit dilution assay. Subclone

5 PG13/YYB-103-13 showed the stably high CAR expression, and was selected to transduce peripheral blood mononuclear cells (PBMC) of human. The transduction efficiency of the PBMC/YYB-103-13 checked with anti-iL-13 monoclonal antibody (BD Pharmingen) using a flow cytometry analysis. The supernatant of PG13/YYB-103-13 cells comprises retrovirus and collected for the genetic modification of PBMC. PBMC were separated using

10 centrifugation by putting whole blood obtained from a healthy human donor into Ficoll Paque (GE Healthcare). The separated PBMC was cultured by adding anti-CD3 monoclonal antibody (eBioscience) 100ng/mL under the condition of Human IL-2 (NOVARTIS) 100IU/mL to activate the T cell fraction (BL Levine, Cancer Gene Therapy, 2015, 22:79-84). After 2 to 3 days activation, most of the cells were T cells, and comprised natural killer

15 cells at a ratio of 0-2%. After 2 to 3 days activation step, the T cells were subject to transduction two times over 2 days using retroviral supernatant and were washed, and then the cells were proliferated for 4 to 7 days in a flask. The cells were cultured in a stirring platform device (WAVE bio-reactor system) for 12 to 14 days. IL-2 was maintained in the amount of 100IU/mL. The CAR-T cell modified in such manner was used for the analysis experiment

20 (Figure 4).

Experimental Example 1: Check for the CAR expression rate of the T cell surface transformed to a chimeric antigen receptor

Experimental method (flow cytometric analysis)

For flow cytometry (>30,000 events), BD LSRII equipment (Becton Dickinson) and BD FACSDiva software (Becton Dickinson) were used. Specifically, before adding a PE-conjugated anti-human IL-13 monoclonal antibody (BD Pharmingen), the cell was washed once with PBS containing 2% bovine serum albumin. After washing, the cell was reacted with the respective antibodies for 30 minutes at 4°C in the state where light was blocked and then washed once, and thereafter, the expression rate of the transduced T cell surface CAR was checked. In addition, in order to verify the cell surface expression of IL13R α 2 and IL13R α 1, anti-human IL13R α antibody (R&D systems), donkey anti-goat IgG phycoerythrin secondary antibody (R&D systems), and anti-human IL13R α phycoerythrin (R&D systems) were used, and as a control, isotype antibody was comprised.

Experimental result

In order to verify that IL13R α 2-specific CAR(YYB-103, IL13.E11K.R107K.TNFRSF9.CD3 ζ ; YYB-103A, IL13.E11K.R64D.S67D.R107K.28.TNFRSF9.CD3 ζ ;YYB-103B, IL13.E11K.R107K.28.TNFRSF9.CD3 ζ) produced in Example 1 was expressed on the T cell

surface, T cell cultivation was carried out for 12 - 14 days according to Example 2 and then the flow cytometric analysis was carried out according to the experimental method. As the result of the analysis, the expression rates of the chimeric antigen receptors expressed on the living T cell surface were 90.5% to 92.8% in the seven (7) blood donors. When the cultivation was maintained, the expression of IL13R α 2-specific chimeric antigen receptor was stably maintained for 4 weeks, without additional T cell activation or transduction. In addition, in the cultured cell, the ratios of entire T cell, CD4 T cell, CD8 T cell, B cell, and Monocyte were analyzed. As the result, it was confirmed that B cell existed in the amount of 0.5-1.2%, and no Monocyte exists.

Example 3: Measurement of cytotoxicity and IFN- γ secretion of the T cell transformed to 2nd generation (YYB-103, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ) and 3rd generation (YYB-103A, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ) chimeric antigen receptors specifically binding to IL13R α 2 overexpressed in cancer cell

IL13R α 2-specific cytotoxicity and IFN- γ secretion were measured using the CAR-T cell produced in Example 2. In order to measure IL13R α 2-specific cytotoxicity and IFN- γ secretion, U251 that is a glioblastoma human cell line overexpressing IL13R α 2, and primary HUVEC that does not express IL13R α 2, as a normal cell control, were used.

Experimental Example 1: Cytotoxicity check for glioblastoma overexpressing

IL13R α 2

Experimental method

In order to measure cytotoxicity of IL13R α 2-specific CAR-T cell effector (IL13R α 2-specific CAR⁺ T cell effector), cytotoxicity assay was carried out using a DELFIA (Perkin Elmer) kit. Specifically, CAR-T cell effector cells were used 12 to 14 days after the cell activation to anti-CD3, and the experiment was carried out three times under the condition where the effector cell was put in a 96 well plate in which IL13R α 2 target cell existed at a ratio of 5:1 (effector:target) and a ratio of 0.625:1 (effector:target) and reacted for 2 hours at 37°C. In the 96 well plate used in this analysis experiment, 5,000 target cells were added per well, and U251, which is a glioblastoma cell line overexpressing IL13R α 2, was used as the used target cell, and primary HUVEC was used as a normal cell control.

Experimental result

It was analyzed whether the target cancer cell (U251) overexpressing IL13R α 2 was effectively killed by IL13R α 2-specific CAR(YYB-103, IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ ;YYB-103A, IL13.E11K.R64D.S67D.R107K.28.TNFRSF9.CD3 ζ ; YYB-103B, IL13.E11K.R107K.28.TNFRSF9.CD3 ζ) T cells produced according to the present invention. As the experimental method, the method of comparing and analyzing cytotoxicity by culturing the target cancer cell (U251) and the normal cell (HuVEC) aforementioned together with the

respective activated CAR-T cell was used. As illustrated in Figure 5, in all cases, the result was obtained that when CAR specific to IL13R α 2 was expressed, the CAR expression induced the killing of glioblastoma U251 cell expressing IL13R α 2 at a high level, as compared to the activated T cell that was not transduced (Figure 5). Specifically, in the case of the T cell expressing YYB-103(IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ), YYB-103A(IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ), and YYB-103B(IL13.E11K.R107K.28TNFRSF9.CD3 ζ) CAR produced in Example 2 of the present invention, as the E:T ratio increased, cytotoxicity gradually increased; however, in the case of T cell that did not express CAR, cytotoxicity rarely increased. In addition, as the result of comparing YYB-103B(IL13.E11K.R107K.28.TNFRSF9.CD3 ζ) CAR, in which two amino acids of IL13 were substituted, and YYB-103(IL13.E11K.R64D.S67D.R107K.TNFRSF9.CD3 ζ) and YYB-103A(IL13.E11K.R64D.S67D.R107K.28.TNFRSF9.CD3 ζ), in which four amino acids of IL13 were substituted, which were used in order to impart higher antigen affinity, in the case of YYB-103B in which only two amino acids were substituted, 67.4% of cytotoxicity was shown at the E:T ratio of 5:1, but when YYB-103 and YYB-103A in which mutant IL13.E11K.R64D.S67D.R107K in which four amino acids of IL13 were substituted were used, 85.6% and 87.7% of cytotoxicity were shown, respectively. This shows that cytotoxicity of T-cell in which mutant IL13.E11K.R64D.S67D.R107K in which four amino acids of IL13 were substituted was introduced is superior in both 2nd generation and 3rd generation as

compared to cytotoxicity of T-cell in which mutant IL13.E11K.R107K in which two amino acids of IL13 were substituted was introduced.

From the experimental result of using, as a normal cell control, HUVEC cell which does not express IL13R α 2 but minimally expresses IL13R α 1, as an object to be compared with the target cells, it was confirmed that the CAR-T cell (12.3-14% cytotoxicity) specific to IL13R α 2 has very weak cytotoxicity (Figure 5). This shows that due to the property of the HUVEC cell which expresses IL13R α 1 and does not express IL13R α 2, the chimeric antigen receptor used in the experiment specifically binds to IL13R α 2. Through the present experimental example, it was demonstrated that IL13R α 2-specific chimeric antigen receptor T cell does not exhibit toxicity to a normal cell (HUVEC) and can significantly kill the target cancer cell (U251) expressing IL13R α 2.

Experimental Example 2: Measurement of anticancer activity change according to CAR expression rate

Experimental method

In order to measure the anticancer activity change according to the expression rate of IL13R α 2-specific CAR, the cytotoxicity analysis was carried out. Specifically, 2nd Generation IL13.E11K.R64D.S67D.R107K.TNFSFR9.CD3 ζ , which is YYB-103, was used as an effector cell for CAR-T cell, and U251 cell line overexpressing IL13R α 2 was used as a

Target cell. For the cytotoxicity analysis, the ratio of the effector cell and the target cell was 0.625:1 and 5:1, and the ratio of T-cell expressing CAR was 0-70%. The detailed method of the cytotoxicity analysis is the same as the experimental method of Experimental Example 2.

5 Experimental Result

In case where T cell expressing IL13R α 2-specific CAR did not exist, 16.4% and 2.5% of cytotoxicity were shown respectively at the ratio of 5:1 and 0.625:1. However, it can be shown that as the ratio of the T cells expressing IL13R α 2-specific CAR increased, the cytotoxicity increased, and it was demonstrated that when the ratio of the T cells expressing
10 IL13R α 2-specific CAR was 70%, 86% and 26% of the cytotoxicity were shown respectively at the ratios of 5:1 and 0.625:1, and thus IL13R α 2-specific chimeric antigen receptor T cell can kill IL13R α 2-specific target cancer cell (U251) (Figure 6).

Experimental Example 3: Check for the production of cytokine (IFN- γ) of T cells
15 transformed to IL13R α 2-specific chimeric antigen receptor

Experimental method

200ul of a culture medium was put per well in 96 well tissue culture plate, and a target cell (1×10^5) was added. In order to measure cytotoxicity according to CAR expression rate, untransduced activated T cell and 10-70% of CAR-T cell specific to IL13R α 2 were put in the
20 prepared 96 well tissue culture plate with the effector (1×10^5), and cultured at the same time

through the duplicate experiment. In addition, in order to verify whether the CAR-T cell shows number-dependent anticancer activity increase, serial dilution was performed from 7500 CAR-T and then put into the effector and cultured at the same time through the duplicate experiment. After 19 hours from the cultivation, the IFN- γ analysis experiment was carried out using the culture supernatant with ELISA analyzer (R&D systems) according to the guidelines of the analyzer manufacturer (Figures 7 and 8).

Experimental result

Generally, the activated T cell generates cytokine that is helpful in its growth and activation, and among them, IFN- γ is secreted by CD8 cell, CD4 T cell and NK cell, etc. and serves an important role in the inherent immune and adaptive immune responses. In particular, this serves an important role in moving T cell to the tumor site as well as inhibiting occurrence of cancer. Through the present experimental example, it was demonstrated whether the generation of IFN- γ is increased when the T cell expressing IL13R α 2-specific CAR met a target cell. According to the experimental method, the T cell expressing IL13R α 2-specific CAR was cultured at the same time as the target cell (HUVEC cell, U251 cell), and then IFN- γ was quantified through the ELISA analysis.

Figure 7 shows increased IFN- γ when binding to IL13R α 2 antigen according to the transduction ratio of the produced chimeric antigen receptor, and it can be understood that the

generation aspects of IFN- γ vary depending on the ratio of the CAR-T cell. In the case of using U251 which is the target cancer cell, the T cell in which the chimeric antigen receptor was untransduced rarely generated IFN- γ . In the case of the T cell in which the chimeric antigen receptor was transduced, the generation of IFN- γ increased by up to 30% ratio, and given that the generation was not increased anymore, it is determined that 30% ratio of the CAR-T cell is sufficient to kill the target cancer cell. Given that in the case of HUVEC which is a cell line that does not overexpress IL13R α 2, even if the ratio of CAR-T increases, the generation of IFN- γ does not increase, it seems that the generation of IFN- γ by CAR-T is specific to IL13R α 2 antigen. Fig. 8 shows increased IFN- γ according to the number of CAR+T cells in two donors, YY6 and YY7, as the number of cells increased, IFN- γ increased. This shows that in killing the cancer cell, the CAR-T cell is dependent on the number of cells.

Example 4: Evaluation of *in vivo* efficacy using YYB-103

In order to evaluate whether YYB-103 actually exhibits efficacy *in vivo*, a cancer cell was subcutaneously injected into a nude mouse to induce tumor, and after treating with YYB-103, the change of the tumor size and the persistence of CAR-T cell in the tumor tissue was confirmed.

Experimental Example 1: Production of a tumor nude mouse using U251 cell line and check for efficacy of YYB-103

The U251 cell line was subcutaneously injected into a nude mouse. After 9 days, control PBS and treatment group YYB-103 were intravenously administered once. Temozolomide (TMZ) and IL-2 were intraperitoneally and intravenously administered into the control group and the experimental group once a day for four days. The size of the tumors was measured after 12 days treatment, and after 15 days treatment, a postmortem was carried out for the measurement of the weight of the tumor tissue and the histologic analysis (Figure 9)

Experimental Result

As the result of measuring the size of the tumor after 12 days treatment to measure efficacy of YYB-103 which was administered into the established subcutaneous tumor nude mouse animal model, in the control group, the size of the tumor was reduced by about 44% from 234.8 mm³ to 132.4 mm³. However, in the case of administering YYB-103 as the treatment group, the size of the tumor was reduced by about 78% from 288.2 mm³ to 64.6 mm³. From this, it can be seen that the treatment group showed the therapeutic effect about 1.8 times as compared to the control group (Figure 9B). As the result of the measurement of the weight of tumor tissue, obtained by carrying out a postmortem after 15 days treatment, it can be seen that the weight of the tumor tissue of the nude mouse treated with the treatment group, YYB-103, was lighter than the weight of the tumor tissue of the mouse treated with the control group (Figure 9C). Together with this, when treated with YYB-103, it showed that

angiogenesis is inhibited in the tumor tissue, unlike the tumor tissue treated with the control group (Figure 11A and Figure 11B).

In order to verify that YYB-103 persists in the tumor tissue after 15 days treatment, staining was carried out using an anti-human CD3 antibody which is human T cell marker. As the result, it showed that the tumor tissue treated with the control group was not stained because the mouse was free of human T cell (Figure 10A).

It was confirmed that the tumor tissue treated with YYB-103, numerous human T cells existed, and this directly gave an influence on the reduction of the size of the tumor treated with YYB-103 (Figure 10B).

As the result of observing the tumor tissue by H&E staining on the tumor tissue after 15 days treatment, it is seen that in the group that was not treated with YYB-103, many blood vessels were observed. Thus, it seems that due to YYB-103, angiogenesis is inhibited in the tumor site, which results in less aggressive tumor (Figure 11A & Figure 11B).

Example 5: Construction of CAR capable of recognizing various solid tumors and angiogenic blood vessels, and production of PG13 cell line stably expressing CAR.

If angiogenesis which allows new blood vessel to grow in the tumor site is inhibited, the transition and growth of the cancer cell can be inhibited. Successful anti-cancer CAR therapies require not only antigen-specific CAR-T cells but also accessing CAR-T cells to cancer cells and maintaining CAR-T cell function in the immunosuppressive tumor microenvironment. Therefore, anti-angiogenic CAR was produced in order to achieve the object (Figure 12A).

CAR targeting EGFRvIII which is major tumor antigen of glioblastoma, lung cancer, etc. was produced (Figure 13A).

EphA2 (Membrane-bound erythropoietin-producing hepatocellular receptor tyrosine kinase class A2) is overexpressed in breast cancer, prostate cancer, bladder cancer, skin cancer, lung cancer, ovarian cancer, and brain cancer, etc., and thus CAR targeting EphA2 was produced (Figure 14A).

Integrin alpha(V) beta(3) ($\alpha V\beta 3$), which is glycoprotein membrane receptor, is highly expressed in activated tumor epithelial cell. CAR targeting $\alpha V\beta 3$ which is a resistant marker of carcinoma stemness and receptor tyrosine kinase inhibitors (RTKIs) such as erlotinib of pancreatic cancer, lung cancer and breast cancer was produced (Figure 15A).

GPC1 is important for efficient growth, transition and angiogenesis of cancer cell, and GPC1 is overexpressed in pancreatic cancer, breast cancer, glioblastoma (Figure 16A).

Experimental Example 1: Check for CAR expression rate on PG13 cell surface transformed to CAR capable of recognizing Angiogenic blood vessels, EGFRvIII, EphA2, Integrin $\alpha V\beta 3$ or GPC1

Experimental method (flow cytometric analysis)

For flow cytometry (>30,000 events), BD LSRII equipment (Becton Dickinson) and BD FACSDiva software (Becton Dickinson) were used. Specifically, before adding an antibody, the cell was washed once with PBS containing 2% bovine serum albumin. After washing, the cell was reacted with the respective antibodies for 30 minutes at 4°C in the state where light was blocked and then washed once, and checked the CAR expression rate on PG13 cell surface transformed to CAR, anti-human Fibronectin monoclonal antibody, PE-conjugated anti-human EphA2 monoclonal antibody (R&D Systems) PE-conjugated anti-human $\alpha v \beta 3$ monoclonal antibody (BioLegend) was used, and in the case of the antibody where fluorescence is not combined, PE conjugated anti-mouse IgG1 monoclonal antibody (Santa Cruz Biotechnology) or donkey anti-goat IgG phycoerythrin secondary antibody (R&D systems) were additionally used to conduct fluorescence staining.

Experimental result

As the result of confirming the expression rates of the respective CARs in the transduced PG13 cell line, it was shown that chimeric antigen receptor is expressed on the surface of almost of living PG13 cell lines (Figure 12B, Figure 13B, Figure 14B, Figure 15B and Figure 16B).

INDUSTRIAL APPLICABILITY

The present invention relates to CAR-T cells that have been rapidly developed in the cancer treatment field, and is applicable to the medical industry in the patient-specific cancer treatment field.

Sequence Listing Free Text

SEQ ID NO. 1 {*Sequence of antigen binding wild type IL-13 domain binding to IL13R α 2*}

Length: 112

Type: ligand protein

Name: human

Sequence:

GPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMYCAALES LINVSGCSAI
EKTQRMLSGFCPHKVSA GQFSSLHVRDTKIEVAQFVKDLLHLKKLFREGQFN

SEQ ID NO. 2 {antigen binding domain capable of binding to an antigen associated with an

angiogenic activity}

Length: 92

Type: ligand protein

Name: human

5 Sequence:

EVVAATPTSLLISWRHPHPTRYRITYGETGGNSPVQEFTVLQPPSTATISGLKPGVD

YTITVYAVVERNGRELNT PPISINYRTHHHHHH

SEQ ID NO. 3 {*antigen binding domain binding to EGFRvIII*}

Length: 252

10 Type: scFv protein

Name: human

Sequence:

QVQLQESGGGLVKPGGSLKLSCAASGFTFSKFGMSWVRQTPDKRLEWVASISTGGYN

TFYSDNVKGRFTISRDNKNTLYLQMSSLKSEDAMYYCARGYSSTSFAMDYWGQG

15 TMVTVSSGSTSGSGKPGSGEGSDIQMTQSPSSLSASVGDRVTITCMTSTDIDDDMNWY

QQKPGKTPKLLIYEGNTLRPGVPSRFSGSGSGTDFITISLQPEDATYYCLQSFNV

PLTFGGGTKVEIKEQKLISEEDL

SEQ ID NO. 4 {*antigen binding domain binding to EphA2*}

Length: 141

20 Type: ligand protein

Name: human

Sequence:

DRHTVFWNSSNPKFRNEDYTIHVQLNDYVDIICPHYEDHSVADAAMEQYILYLVEHE
EYQLCQPQSKDQVRWQCN

5 RPSAKHGPEKLSEKFQRFTAFA LAKEFKAGHSYYYISKPIHQHEDRCLRLKVTVSSEQ
KLISEEDL

SEQ ID NO. 5 *{antigen binding domain binding to $\alpha V\beta 3$ }*

Length: 104

Type: ligand protein

10 Name: human

Sequence:

VSDVPRDLEVVAATPTSLLISWDAPAVTVRYRITYGETGGNSPVQEFTVPGSKSTATI
SGLKPGVDYTITVYAVTPRGDWNESKPI SIN YRTEQKLISEEDL

SEQ ID NO. 6 *{antigen binding domain binding to glypican1}*

15 Length: 418

Type: ligand protein

Name: human

Sequence:

TSPCDNFDCQNGAQCIVRINEPICQCLPGYQGEKCEKLVSVNFINKESYLQIPSAKVRP

20 QTNITLQIATDEDSGILLYKGDKDHI AVELYRGRVRASYDTGSHPASAIYSVETINDG

NFHIVELLALDQSLSLSDGGNPKIITNLSKQSTLNFDSPLYVGGMPGKSNVASLRQAP
GQNGTSFHGCIRNLYINSELQDFQKVPMQTGILPGCEPCHKKVCAHGTCQPSSQAGFT
CECQEGWMGPLCDQRTNDPCLGNKCVHGTCLPINAFSYSCKCLEGHGGVLCDEEED
LFNPCQAIKCKHGKCRLSGLGQPYCECSSGYTGDSCDREISCRGERIRDYYQKQQGY

5 AACQTTKKVSRLECRGGCAGGQCCGPLRSKRRKYSFECTDGSSFVDEVEKVVKCGC
TRCVSEQKLISEEDL

SEQ ID NO. 7 *{Wild type CD28}*

Length: 41

Type: protein

10 Name: human

Sequence:

RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS

SEQ ID NO. 8 *{TNFRSF9}*

Length: 42

15 Type: protein

Name: human

Sequence:

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL

SEQ ID NO. 9 *{hinge region sequence -1}*

20 Length: 47

Type: protein

Name: human

Sequence:

KPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD

5 SEQ ID NO. 10 *{hinge region sequence-2}*

Length: 45

Type: protein

Name: human

Sequence:

10 KPTTTPAPRPPTPAPTIASQPLSLRPEAARPAAGGAVHTRGLDFA

SEQ ID NO. 11 *{transmembrane domain sequence-1}*

Length: 21

Type: protein

Name: human

15 Sequence:

IYIWAPLAGTCGVLLLSLVIT

SEQ ID NO. 12 *{transmembrane domain sequence-2}*

Length: 23

Type: protein

20 Name: human

Sequence:

LAYLLDGILFIYGVILTALFLRV

SEQ ID NO. 13 {CD3 ζ comprising extra glutamine}

Length: 113

5 Type: protein

Name: human

Sequence:

RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQ

EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPP

10 R

SEQ ID NO. 14 {YYB 103}

Length: 359

Type: protein

Name: human

15 Sequence:

MGWSCILFLVATATGVHSGPVPSTALRKLIEELVNITQNQKAPLCNGSMVWSINLT

AGMYCAALESLINVSGCSAIEKTQDMLDGFCPHKVSAGQFSSLHVRDTKIEVAQFVK

DLLLHLKKLFKEGQFNGGGPRKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH

TRGLDFACDIYIWAPLAGTCGVLLLSLVITKRGRKKLLYIFKQPFMRPVQTTQEEDGC

20 SCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP

EMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT

KDTYDALHMQALPPR

SEQ ID NO. 15 {YYB 103A}

Length: 400

5 Type: protein

Name: human

Sequence:

MGWSCILFLVATATGVHSGPVPPSTALRKLIIEELVNITQNQKAPLCNGSMVWSINLT

AGMYCAALESLINVSGCSAIEKTQDMLDGFCHKVSAGQFSSLHVRDTKIEVAQFVK

10 DLLLHLKKLFKEGQFNGGGPRKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVH

TRGLDFACDIYWAPLAGTCGVLLLSLVITRSKRSRGGHSDYMNMTPRRPGPTRKHY

QPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRV

KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEG

LYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

15 SEQ ID NO. 16 {YYB-103B, IL13(E11K.R107K).29.TNFRSF9.CD3ζ}

Length: 400

Type: protein

Name: human

Sequence:

20 MGWSCILFLVATATGVHSGPVPPSTALRKLIIEELVNITQNQKAPLCNGSMVWSINLT

AGMYCAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKD
LLLHLKKLFKEGQFNNGGPRKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT
RGLDFACDIYIWAPLAGTCGVLLLLSLVITRSKRSRGGHSDYMNMTPRRPGPTRKHYP
YAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKF
5 SRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGL
YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO. 17 {YYB 104}

Length: 339

Type: protein

10 Name: human

Sequence:

MGWSCILFLVATATGVHSEVVAATPTSLLISWRHPHPTRYRITYGETGGNSPVQEF
TVLQPPSTATISGLKPGVDYTITVYAVVERNGRELNTPPISINYRTHHHHHHGGGPRKP
TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVL
15 LLSLVITKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADA
PAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQK
DKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO. 18 {YYB 104-1}

Length: 308

20 Type: protein

Name: human

Sequence:

MGWSCILFLVATATGVHSEVVAATPTSLLISWRHPHPTRYRITYGETGGNSPVQEF
TVLQPPSTATISGLKPGVDYTITVYAVVERNGRELNTPPISINYRTHHHHHHGGGPRKP
5 TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVL
LLSLVITRSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLLY
IFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELN
LGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGE
RRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

10 SEQ ID NO. 19 {YYB 105}

Length: 497

Type: protein

Name: human

Sequence:

15 MGWSCILFLVATATGVHSQVQLQESGGGLVKPGGSLKLSCAASGFTFSKFGMSWVR
QTPDKRLEWVASISTGGYNTFYSDNVKGRFTISRDNAKNTLYLQMSSLKSEDTAMYY
CARGYSSTSFAMDYWGQGTMTVSSGSTSGSGKPGSGEGSDIQMTQSPSSLSASVGD
RVTITCMTSTDIDDDMNWYQQKPGKTPKLLIYEGNTPRGVPSRFSGSGSGTDFITIS
SLQPEDIATYYCLQSFNVPLTFGGGKVEIKEQKLISEEDLGGGPRKPTTTPAPRPPTPA
20 PTIASQPLSLRPEAARPAAGGAVHTRGLDFALAYLLDGILFIYGVILTALFLRVKRGRK

KLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELKFSRSADAPAYQQGQNQLYNE
LNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMK
GERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO. 20 {YYB 105-1}

5 Length: 538

Type: protein

Name: human

Sequence:

MGWSCILFLVATATGVHSQVQLQESGGGLVKPGGSLKLSCAASGFTFSKFGMSWVR
10 QTPDKRLEWVASISTGGYNTFYSDNVKGRFTISRDNKNTLYLQMSSLKSEDTAMYY
CARGYSSTSFAMDYWGQGTMTVSSGSTSGSGKPGSGEGSDIQMTQSPSSLSASVGD
RVTITCMTSTDIDDDMNWYQQKPGKTPKLLIYEGNTPRGVPSRFSGSGSGTDFIFTIS
SLQPEDIATYYCLQSFNVPLTFGGGKVEIKEQKLISEEDLGGGPRKPTTTPAPRPPTPA
PTIASQPLSLRPEAARPAAGGAVHTRGLDFALAYLLDGILFIYGVILTALFLRVRSKRSR
15 GGHS DYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQT
TQEEDGCSCRFPEEEEEGGCELKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKR
RGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQG
LSTATKDTYDALHMQALPPR

SEQ ID NO. 21 {YYB 106}

20 Length: 388

Type: protein

Name: human

Sequence:

MGWSCILFLVATATGVHSDRHTVFWNSSNPKFRNEDYTIHVQLNDYVDIICPHYEDH

5 SVADAAMEQYILYLVEHEEYQLCQPQSKDQVRWQCNRPSAKHGPEKLSEKFQRFTAF
ALAKEFKAGHSYYYISKPIHQHEDRCLRLKVTVSQGEQKLISEEDLGGGPRKPTTTPAPR
PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT
KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQ
GQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAE
10 AYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQ ALPPR

SEQ ID NO. 22 {YYB 106-1}

Length: 429

Type: protein

Name: human

15 Sequence:

MGWSCILFLVATATGVHSDRHTVFWNSSNPKFRNEDYTIHVQLNDYVDIICPHYEDH

SVADAAMEQYILYLVEHEEYQLCQPQSKDQVRWQCNRPSAKHGPEKLSEKFQRFTAF

ALAKEFKAGHSYYYISKPIHQHEDRCLRLKVTVSQGEQKLISEEDLGGGPRKPTTTPAPR

PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT

20 RSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRSKRGRKKLLYIFKQPFM

RPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREE
YDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKG
HDGLYQGLSTATKDTYDALH MQALPPR

SEQ ID NO. 23 {YYB 107}

5 Length: 351

Type: protein

Name: human

Sequence:

MGWSCILFLVATATGVHSVSDVPRDLEVVAATPTSLLISWDAPAVTVRYRITYGET
10 GGNSPVQEFTVPGSKSTATISGLKPGVDYTITVYAVTPRGDWNESKPI SIN YRTEQKL
ISEEDLGGGPRKPTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY
IWAPLAGTCGVLLLSLVITKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGC
ELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKN
PQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA
15 LPPR

SEQ ID NO. 24 {YYB 107-1}

Length: 392

Type: protein

Name: human

20 Sequence:

MGWSCILFLVATATGVHSVSDVPRDLEVVAATPTSLLISWDAPAVTVRYRITYGET
GGNSPVQEFTVPGSKSTATISGLKPGVDYTITVYAVTPRGDWNESKPI SIN YRTEQKL
ISEEDLGGGPRKPTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIY
IWAPLAGTCGVLLLSLVITRSKRSRGGHSDYMNMTPRRPGPTRKHYPYAPPRDFAA
5 YRSKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCEL RVKFSRSADAPAY
QQGQNQLYNELNLGRREEYDVLDKRRGRDP EMGGKPQRRKNPQEGLYNELQKDKM
AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO. 25 {YYB 108}

Length: 665

10 Type: protein

Name: human

Sequence:

MGWSCILFLVATATGVHSTSPCDNFDCQNGAQCIVRINEPICQCLPGYQGEKCEKLVS
VNFINKESYLQIPSAKVRPQTNITLQIATDEDSGILLYKGDKDHIAVELYRGRVRASYD
15 TGSHPASAIYSVETINDGNFHIVELLALDQSLSLSDGGNPKIITNLSKQSTLNFDSPLY
VGGMPGKSNVASLRQAPGQNGTSFHGCIRNLYINSELQDFQKVPMQTGILPGCEPCH
KKVCAHGTCQPSSQAGFTCECQEGWMGPLCDQRTNDPCLGNKCVHGTCLPINAFSY
SCKCLEGHGGVLCDEEEDLFNPCQAIKCKHKGKRLSGLGQPYCECSSGYTGDSCDREI
SCRGERIRDYYQKQQGYAACQTTKKVSRLECRGGCAGGQCCGPLRSKRRKYSFECT
20 DGSSFVDEVEKVVKCGCTRCVSEQKLISEEDLGGGPRKPTTTTPAPRPPTPAPTIASQPL

SLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITKRGRKKLLYIFK
QPFMRPVQTTQEEDGCSCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLG
RREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERR
RGKGHDGLYQGLSTATKDTYDALHMQALPPR

5 SEQ ID NO. 26 {YYB 108-1}

Length: 706

Type: protein

Name: human

Sequence:

10 MGWSCILFLVATATGVHSTSPCDNFDCQNGAQCIVRINEPICQCLPGYQGEKCEKLVS
VNFINKESYLQIPSAKVRPQTNITLQIATDEDSGILLYKGDKDHIARELYRGRVRASYD
TGSHPASAIYSVETINDGNFHVELLALDQSLSLSDGGNPKIITNLSKQSTLNFDSPY
VGGMPGKSNVASLRQAPGQNGTSFHGCIRNLYINSELQDFQKVPMQTGILPGCEPCH
KKVCAHGTCQPSSQAGFTCECQEGWMGPLCDQRTNDPCLGNKCVHGTCLPINAFSY
15 SCKCLEGHGGVLCDEEEDLFNPCQAIKCKHKGKRLSGLGQPYCECSSGYTGDSCDREI
SCRGERIRDYYQKQQGYAACQTTKKVSRLECRGGCAGGQCCGPLRSKRRKYSFECT
DGSSFVDEVEKVVKCGCTRCVSEQKLISEEDLGGGPRKPTTTPAPRPPTPAPTIASQPL
SLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITRSKRSRGGHSDY
MNMTPRRPGPTRKHYQPYAPPRDFAAYRSKRGRKKLLYIFKQPFMRPVQTTQEEDGC
20 SCRFPEEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDP

EMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT

KDTYDALHMQALPPR

Claims:

1. A chimeric antigen receptor comprising an antigen binding domain; a hinge region; a transmembrane domain; a costimulatory domain; and a cytoplasmic signaling domain,
5 characterized in that the antigen binding domain binds to IL13R α 2,

wherein, in the antigen binding domain, the 11th, 64th, 67th, and 107th positions of the amino acid sequence indicated with Sequence No. 1 are substituted with lysine(K), aspartic acid(D), aspartic acid(D) and lysine(K), respectively.

10 2. The chimeric antigen receptor according to claim 1, characterized in that three glycines are additionally introduced between the antigen binding domain and the hinge region.

3. The chimeric antigen receptor according to claim 1, indicated with Sequence No. 14.

15 4. The chimeric antigen receptor according to claim 1, indicated with Sequence No. 15.

5. CAR-T cell in which the chimeric antigen receptor according to any one of claims 1 to 4 is expressed.

SP102075SGM SEQUENCE LISTING

<110> YOO YOUNG PHARM CO.,LTD.
 <120> CHIMERIC ANTIGEN RECEPTOR AND T CELLS EXPRESSING THE CHIMERIC ANTIGEN RECEPTOR
 <130> SP102075SGM
 <150> 10-2015-0110788
 <151> 2015-08-05
 <160> 26
 <170> KoPatentIn 3.0
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 <211> 112
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 <223> HUMAN

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

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 <211> 92
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 Pro His Phe Pro Thr Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly
 20 25 30
 Gly Asn Ser Pro Val Gln Glu Phe Thr Val Leu Gln Pro Pro Ser Thr
 35 40 45
 Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val
 Page 1

SP102075SGM SEQUENCE LISTING

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65 70 75 80

Ser Ile Asn Tyr Arg Thr His His His His His His
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<220>
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20 25 30

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35 40 45

Ala Ser Ile Ser Thr Gly Gly Tyr Asn Thr Phe Tyr Ser Asp Asn Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Ser Ser Thr Ser Phe Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser Gly Ser Thr Ser Gly Ser Gly Lys
115 120 125

Pro Gly Ser Gly Glu Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Met Thr
145 150 155 160

Ser Thr Asp Ile Asp Asp Asp Met Asn Trp Tyr Gln Gln Lys Pro Gly
165 170 175

Lys Thr Pro Lys Leu Leu Ile Tyr Glu Gly Asn Thr Leu Arg Pro Gly
180 185 190

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Phe
195 200 205

Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Leu
210 215 220

Gln Ser Phe Asn Val Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu
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Ile Lys Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
245 250

SP102075SGM SEQUENCE LISTING

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 Cys Pro His Tyr Glu Asp His Ser₄₀ Val Ala Asp Ala₄₅ Ala Met Glu Gln
 Tyr Ile₅₀ Leu Tyr Leu Val₅₅ Glu His Glu Glu Tyr Gln₆₀ Leu Cys Gln Pro
 Gln Ser Lys Asp Gln Val₇₀ Arg Trp Gln Cys Asn₇₅ Arg Pro Ser Ala Lys₈₀
 His Gly Pro Glu Lys₈₅ Leu Ser Glu Lys Phe₉₀ Gln Arg Phe Thr Ala₉₅ Phe
 Ala Leu Ala Lys₁₀₀ Glu Phe Lys Ala Gly₁₀₅ His Ser Tyr Tyr Tyr₁₁₀ Ile Ser
 Lys Pro Ile₁₁₅ His Gln His Glu Asp₁₂₀ Arg Cys Leu Arg Leu₁₂₅ Lys Val Thr
 Val Ser₁₃₀ Gly Glu Gln Lys Leu₁₃₅ Ile Ser Glu Glu Asp₁₄₀ Leu

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 Arg Ile Thr Tyr Gly Glu Thr Gly₄₀ Gly Asn Ser Pro Val₄₅ Gln Glu Phe
 Thr Val₅₀ Pro Gly Ser Lys Ser₅₅ Thr Ala Thr Ile Ser₆₀ Gly Leu Lys Pro
 Gly Val Asp Tyr Thr Ile₇₀ Thr Val Tyr Ala Val₇₅ Thr Pro Arg Gly Asp₈₀
 Trp Asn Glu Gly Ser₈₅ Lys Pro Ile Ser Ile₉₀ Asn Tyr Arg Thr Glu Gln₉₅

SP102075SGM SEQUENCE LISTING

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

SP102075SGM SEQUENCE LISTING

Glu Asp Leu Phe Asn Pro Cys Gln Ala Ile Lys Cys Lys His Gly Lys
 290 295 300
 Cys Arg Leu Ser Gly Leu Gly Gln Pro Tyr Cys Glu Cys Ser Ser Gly
 305 310 315 320
 Tyr Thr Gly Asp Ser Cys Asp Arg Glu Ile Ser Cys Arg Gly Glu Arg
 325 330 335
 Ile Arg Asp Tyr Tyr Gln Lys Gln Gln Gly Tyr Ala Ala Cys Gln Thr
 340 345 350
 Thr Lys Lys Val Ser Arg Leu Glu Cys Arg Gly Gly Cys Ala Gly Gly
 355 360 365
 Gln Cys Cys Gly Pro Leu Arg Ser Lys Arg Arg Lys Tyr Ser Phe Glu
 370 375 380
 Cys Thr Asp Gly Ser Ser Phe Val Asp Glu Val Glu Lys Val Val Lys
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 405 410 415

Asp Leu

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 <223> HUMAN

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 35 40

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<400> 8
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SP102075SGM SEQUENCE LISTING

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<220>
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 20 25 30
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 35 40 45

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 20 25 30
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 35 40 45

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 <211> 23
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 <223> HUMAN

SP102075SGM SEQUENCE LISTING

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 Thr Ala Leu Phe Leu Arg Val
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 Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
 20 25 30
 Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
 35 40 45
 Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
 50 55 60
 Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
 65 70 75 80
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 85 90 95
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 35 40 45
 Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala
 50 55 60
 Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys
 65 70 75 80

SP102075SGM SEQUENCE LISTING

Thr Gln Asp Met Leu Asp Gly Phe Cys Pro His Lys Val Ser Ala Gly
85 90 95

Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln
100 105 110

Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe Lys Glu Gly
115 120 125

Gln Phe Asn Gly Gly Gly Pro Arg Lys Pro Thr Thr Thr Pro Ala Pro
130 135 140

Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
145 150 155 160

Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
165 170 175

Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
180 185 190

Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Lys Arg Gly Arg
195 200 205

Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln
210 215 220

Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu
225 230 235 240

Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala
245 250 255

Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu
260 265 270

Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp
275 280 285

Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly
290 295 300

Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu
305 310 315 320

Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu
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SP102075SGM SEQUENCE LISTING

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Glu Glu Leu Val Asn Ile Thr Gln Asn Gln Lys Ala Pro Leu Cys Asn
35 40 45
Gly Ser Met Val Trp Ser Ile Asn Leu Thr Ala Gly Met Tyr Cys Ala
50 55 60
Ala Leu Glu Ser Leu Ile Asn Val Ser Gly Cys Ser Ala Ile Glu Lys
65 70 75 80
Thr Gln Asp Met Leu Asp Gly Phe Cys Pro His Lys Val Ser Ala Gly
85 90 95
Gln Phe Ser Ser Leu His Val Arg Asp Thr Lys Ile Glu Val Ala Gln
100 105 110
Phe Val Lys Asp Leu Leu Leu His Leu Lys Lys Leu Phe Lys Glu Gly
115 120 125
Gln Phe Asn Gly Gly Gly Pro Arg Lys Pro Thr Thr Thr Pro Ala Pro
130 135 140
Arg Pro Pro Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu
145 150 155 160
Arg Pro Glu Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg
165 170 175
Gly Leu Asp Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly
180 185 190
Thr Cys Gly Val Leu Leu Leu Ser Leu Val Ile Thr Arg Ser Lys Arg
195 200 205
Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro
210 215 220
Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe
225 230 235 240
Ala Ala Tyr Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe
245 250 255
Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly
260 265 270
Cys Ser Cys Arg Phe Pro Glu Glu Glu Gly Gly Cys Glu Leu Arg
275 280 285
Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
290 295 300
Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
305 310 315 320
Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
325 330 335
Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
340 345 350
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
355 360 365
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
370 375 380

SP102075SGM SEQUENCE LISTING

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

SP102075SGM SEQUENCE LISTING

Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln
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 Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp
 305 310 315 320
 Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro
 325 330 335
 Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
 340 345 350
 Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
 355 360 365
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 370 375 380
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 35 40 45
 Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Leu Gln Pro
 50 55 60
 Pro Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
 65 70 75 80
 Ile Thr Val Tyr Ala Val Val Glu Arg Asn Gly Arg Glu Leu Asn Thr
 85 90 95
 Pro Pro Ile Ser Ile Asn Tyr Arg Thr His His His His His Gly
 100 105 110
 Gly Gly Pro Arg Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
 115 120 125
 Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
 130 135 140
 Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
 145 150 155 160
 Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
 165 170 175
 Leu Leu Leu Ser Leu Val Ile Thr Lys Arg Gly Arg Lys Lys Leu Leu
 180 185 190

SP102075SGM SEQUENCE LISTING

Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu
195 200 205
Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys
210 215 220
Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln
225 230 235 240
Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu
245 250 255
Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly
260 265 270
Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu
275 280 285
Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys
290 295 300
Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu
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35 40 45
Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe Thr Val Leu Gln Pro
50 55 60
Pro Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr
65 70 75 80
Ile Thr Val Tyr Ala Val Val Glu Arg Asn Gly Arg Glu Leu Asn Thr
85 90 95
Pro Pro Ile Ser Ile Asn Tyr Arg Thr His His His His His His Gly
100 105 110
Gly Gly Pro Arg Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr
115 120 125
Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala
130 135 140

SP102075SGM SEQUENCE LISTING

Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe
145 150 155 160
Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val
165 170 175
Leu Leu Leu Ser Leu Val Ile Thr Arg Ser Lys Arg Ser Arg Gly Gly
180 185 190
His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr Arg
195 200 205
Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr Arg
210 215 220
Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe
225 230 235 240
Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg
245 250 255
Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe Ser
260 265 270
Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu Tyr
275 280 285
Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp Lys
290 295 300
Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg Lys
305 310 315 320
Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met Ala
325 330 335
Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly Lys
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Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp Thr
355 360 365
Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
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<220>
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20 25 30
Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
Ser Lys Phe Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu
50 55 60

SP102075SGM SEQUENCE LISTING

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

SP102075SGM SEQUENCE LISTING

420 425 430
 Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln
 435 440 445
 Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu
 450 455 460
 Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr
 465 470 475 480
 Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro
 485 490 495

Arg

<210> 20
 <211> 538
 <212> PRT
 <213> Unknown

<220>
 <223> HUMAN

<400> 20
 Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
 1 5 10 15
 Val His Ser Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Leu Val Lys
 20 25 30
 Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45
 Ser Lys Phe Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu
 50 55 60
 Glu Trp Val Ala Ser Ile Ser Thr Gly Gly Tyr Asn Thr Phe Tyr Ser
 65 70 75 80
 Asp Asn Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
 85 90 95
 Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met
 100 105 110
 Tyr Tyr Cys Ala Arg Gly Tyr Ser Ser Thr Ser Phe Ala Met Asp Tyr
 115 120 125
 Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Ser Thr Ser Gly
 130 135 140
 Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Asp Ile Gln Met Thr Gln
 145 150 155 160
 Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
 165 170 175
 Cys Met Thr Ser Thr Asp Ile Asp Asp Asp Met Asn Trp Tyr Gln Gln
 180 185 190
 Lys Pro Gly Lys Thr Pro Lys Leu Leu Ile Tyr Glu Gly Asn Thr Leu
 195 200 205
 Arg Pro Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp

SP102075SGM SEQUENCE LISTING

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

<210> 21
 <211> 388
 <212> PRT
 <213> Unknown

SP102075SGM SEQUENCE LISTING

<220>

<223> HUMAN

<400> 21

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Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
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Val His Ser Asp Arg His Thr Val Phe Trp Asn Ser Ser Asn Pro Lys
      20      25      30
Phe Arg Asn Glu Asp Tyr Thr Ile His Val Gln Leu Asn Asp Tyr Val
      35      40      45
Asp Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala
 50      55      60
Met Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Glu Tyr Gln Leu
 65      70      75      80
Cys Gln Pro Gln Ser Lys Asp Gln Val Arg Trp Gln Cys Asn Arg Pro
      85      90      95
Ser Ala Lys His Gly Pro Glu Lys Leu Ser Glu Lys Phe Gln Arg Phe
      100      105      110
Thr Ala Phe Ala Leu Ala Lys Glu Phe Lys Ala Gly His Ser Tyr Tyr
      115      120      125
Tyr Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu
      130      135      140
Lys Val Thr Val Ser Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
      145      150      155      160
Gly Gly Gly Pro Arg Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
      165      170      175
Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
      180      185      190
Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
      195      200      205
Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
      210      215      220
Val Leu Leu Leu Ser Leu Val Ile Thr Lys Arg Gly Arg Lys Lys Leu
      225      230      235      240
Leu Tyr Ile Phe Lys Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln
      245      250      255
Glu Glu Asp Gly Cys Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly
      260      265      270
Cys Glu Leu Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr
      275      280      285
Gln Gln Gly Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg
      290      295      300
Glu Glu Tyr Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met
      305      310      315      320
Gly Gly Lys Pro Gln Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn
      325      330      335

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SP102075SGM SEQUENCE LISTING

Glu Leu Gln Lys Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met
 340 345 350
 Lys Gly Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly
 355 360 365
 Leu Ser Thr Ala Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala
 370 375 380
 Leu Pro Pro Arg
 385

<210> 22
 <211> 429
 <212> PRT
 <213> Unknown

<220>
 <223> HUMAN

<400> 22
 Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
 1 5 10 15
 Val His Ser Asp Arg His Thr Val Phe Trp Asn Ser Ser Asn Pro Lys
 20 25 30
 Phe Arg Asn Glu Asp Tyr Thr Ile His Val Gln Leu Asn Asp Tyr Val
 35 40 45
 Asp Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala
 50 55 60
 Met Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Glu Tyr Gln Leu
 65 70 75 80
 Cys Gln Pro Gln Ser Lys Asp Gln Val Arg Trp Gln Cys Asn Arg Pro
 85 90 95
 Ser Ala Lys His Gly Pro Glu Lys Leu Ser Glu Lys Phe Gln Arg Phe
 100 105 110
 Thr Ala Phe Ala Leu Ala Lys Glu Phe Lys Ala Gly His Ser Tyr Tyr
 115 120 125
 Tyr Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu
 130 135 140
 Lys Val Thr Val Ser Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
 145 150 155 160
 Gly Gly Gly Pro Arg Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro
 165 170 175
 Thr Pro Ala Pro Thr Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu
 180 185 190
 Ala Cys Arg Pro Ala Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp
 195 200 205
 Phe Ala Cys Asp Ile Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly
 210 215 220
 Val Leu Leu Leu Ser Leu Val Ile Thr Arg Ser Lys Arg Ser Arg Gly
 225 230 235 240

SP102075SGM SEQUENCE LISTING

Gly His Ser Asp Tyr Met Asn Met Thr Pro Arg Arg Pro Gly Pro Thr
245 250 255
Arg Lys His Tyr Gln Pro Tyr Ala Pro Pro Arg Asp Phe Ala Ala Tyr
260 265 270
Arg Ser Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro
275 280 285
Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys
290 295 300
Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val Lys Phe
305 310 315 320
Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn Gln Leu
325 330 335
Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val Leu Asp
340 345 350
Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln Arg Arg
355 360 365
Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met
370 375 380
Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg Arg Gly
385 390 395 400
Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr Lys Asp
405 410 415
Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
420 425

<210> 23
<211> 351
<212> PRT
<213> Unknown

<220>
<223> HUMAN

<400> 23
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15
Val His Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala
20 25 30
Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val
35 40 45
Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val
50 55 60
Gln Glu Phe Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly
65 70 75 80
Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Pro
85 90 95
Arg Gly Asp Trp Asn Glu Gly Ser Lys Pro Ile Ser Ile Asn Tyr Arg
100 105 110

SP102075SGM SEQUENCE LISTING

Thr Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gly Gly Gly Pro Arg
115 120 125

Lys Pro Thr Thr Thr Pro Ala Pro Arg Pro Pro Thr Pro Ala Pro Thr
130 135 140

Ile Ala Ser Gln Pro Leu Ser Leu Arg Pro Glu Ala Cys Arg Pro Ala
145 150 155 160

Ala Gly Gly Ala Val His Thr Arg Gly Leu Asp Phe Ala Cys Asp Ile
165 170 175

Tyr Ile Trp Ala Pro Leu Ala Gly Thr Cys Gly Val Leu Leu Leu Ser
180 185 190

Leu Val Ile Thr Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys
195 200 205

Gln Pro Phe Met Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys
210 215 220

Ser Cys Arg Phe Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu Arg Val
225 230 235 240

Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly Gln Asn
245 250 255

Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr Asp Val
260 265 270

Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys Pro Gln
275 280 285

Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp
290 295 300

Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg Arg
305 310 315 320

Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala Thr
325 330 335

Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
340 345 350

<210> 24
<211> 392
<212> PRT
<213> Unknown

<220>
<223> HUMAN

<400> 24
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala
20 25 30

Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val
35 40 45

Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val

SP102075SGM SEQUENCE LISTING

50	55	60	
Gln 65	Glu Phe Thr Val Pro 70	Gly Ser Lys Ser Thr 75	Ala Thr Ile Ser Gly 80
Leu	Lys Pro Gly Val 85	Asp Tyr Thr Ile Thr 90	Val Tyr Ala Val Thr 95
Arg	Gly Asp Trp 100	Asn Glu Gly Ser Lys 105	Pro Ile Ser Ile Asn 110
Thr	Glu Gln 115	Lys Leu Ile Ser Glu 120	Glu Asp Leu Gly Gly 125
Lys	Pro Thr Thr Thr 130	Pro Ala 135	Pro Arg Pro Pro Thr 140
Ile 145	Ala Ser Gln Pro Leu 150	Ser Leu Arg Pro Glu 155	Ala Cys Arg Pro Ala 160
Ala	Gly Gly Ala Val 165	His Thr Arg Gly Leu 170	Asp Phe Ala Cys Asp 175
Tyr	Ile Trp Ala 180	Pro Leu Ala Gly Thr 185	Cys Gly Val Leu 190
Leu	Val Ile 195	Thr Arg Ser Lys Arg 200	Ser Arg Gly Gly His 205
Met	Asn Met Thr Pro Arg Arg 215	Pro Gly Pro Thr Arg 220	Lys His Tyr Gln
Pro 225	Tyr Ala Pro Pro Arg 230	Asp Phe Ala Ala Tyr 235	Arg Ser Lys Arg Gly 240
Arg	Lys Lys Leu Leu 245	Tyr Ile Phe Lys Gln 250	Pro Phe Met Arg Pro 255
Gln	Thr Thr Gln 260	Glu Glu Asp Gly Cys 265	Ser Cys Arg Phe Pro 270
Glu	Glu Gly Gly 275	Cys Glu Leu Arg Val 280	Lys Phe Ser Arg 285
Ala	Pro Ala Tyr Gln Gln 295	Gly Gln Asn Gln Leu 300	Tyr Asn Glu Leu Asn
Leu 305	Gly Arg Arg Glu Glu 310	Tyr Asp Val Leu Asp 315	Lys Arg Arg Gly Arg 320
Asp	Pro Glu Met Gly 325	Gly Lys Pro Gln Arg 330	Arg Lys Asn Pro Gln 335
Gly	Leu Tyr Asn 340	Glu Leu Gln Lys Asp 345	Lys Met Ala Glu Ala 350
Glu	Ile Gly Met Lys Gly Glu 360	Arg Arg Arg Gly Lys 365	Gly His Asp Gly
Leu	Tyr Gln Gly Leu Ser Thr 375	Ala Thr Lys Asp Thr 380	Tyr Asp Ala Leu
His 385	Met Gln Ala Leu Pro 390	Pro Arg	

<210> 25
<211> 665

SP102075SGM SEQUENCE LISTING

<212> PRT
<213> Unknown

<220>
<223> HUMAN

<400> 25
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
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Val His Ser Thr Ser Pro Cys Asp Asn Phe Asp Cys Gln Asn Gly Ala
20 25 30
Gln Cys Ile Val Arg Ile Asn Glu Pro Ile Cys Gln Cys Leu Pro Gly
35 40 45
Tyr Gln Gly Glu Lys Cys Glu Lys Leu Val Ser Val Asn Phe Ile Asn
50 55 60
Lys Glu Ser Tyr Leu Gln Ile Pro Ser Ala Lys Val Arg Pro Gln Thr
65 70 75 80
Asn Ile Thr Leu Gln Ile Ala Thr Asp Glu Asp Ser Gly Ile Leu Leu
85 90 95
Tyr Lys Gly Asp Lys Asp His Ile Ala Val Glu Leu Tyr Arg Gly Arg
100 105 110
Val Arg Ala Ser Tyr Asp Thr Gly Ser His Pro Ala Ser Ala Ile Tyr
115 120 125
Ser Val Glu Thr Ile Asn Asp Gly Asn Phe His Ile Val Glu Leu Leu
130 135 140
Ala Leu Asp Gln Ser Leu Ser Leu Ser Val Asp Gly Gly Asn Pro Lys
145 150 155 160
Ile Ile Thr Asn Leu Ser Lys Gln Ser Thr Leu Asn Phe Asp Ser Pro
165 170 175
Leu Tyr Val Gly Gly Met Pro Gly Lys Ser Asn Val Ala Ser Leu Arg
180 185 190
Gln Ala Pro Gly Gln Asn Gly Thr Ser Phe His Gly Cys Ile Arg Asn
195 200 205
Leu Tyr Ile Asn Ser Glu Leu Gln Asp Phe Gln Lys Val Pro Met Gln
210 215 220
Thr Gly Ile Leu Pro Gly Cys Glu Pro Cys His Lys Lys Val Cys Ala
225 230 235 240
His Gly Thr Cys Gln Pro Ser Ser Gln Ala Gly Phe Thr Cys Glu Cys
245 250 255
Gln Glu Gly Trp Met Gly Pro Leu Cys Asp Gln Arg Thr Asn Asp Pro
260 265 270
Cys Leu Gly Asn Lys Cys Val His Gly Thr Cys Leu Pro Ile Asn Ala
275 280 285
Phe Ser Tyr Ser Cys Lys Cys Leu Glu Gly His Gly Gly Val Leu Cys
290 295 300
Asp Glu Glu Glu Asp Leu Phe Asn Pro Cys Gln Ala Ile Lys Cys Lys
305 310 315 320

SP102075SGM SEQUENCE LISTING

His Gly Lys Cys Arg 325 Leu Ser Gly Leu Gly 330 Gln Pro Tyr Cys Glu 335 Cys
 Ser Ser Gly Tyr 340 Thr Gly Asp Ser Cys 345 Asp Arg Glu Ile Ser 350 Cys Arg
 Gly Glu Arg 355 Ile Arg Asp Tyr Tyr 360 Gln Lys Gln Gln Gly 365 Tyr Ala Ala
 Cys Gln 370 Thr Thr Lys Lys Val 375 Ser Arg Leu Glu Cys 380 Arg Gly Gly Cys
 Ala Gly Gly Gln Cys Cys 390 Gly Pro Leu Arg Ser 395 Lys Arg Arg Lys Tyr 400
 Ser Phe Glu Cys Thr 405 Asp Gly Ser Ser Phe 410 Val Asp Glu Val Glu 415 Lys
 Val Val Lys Cys 420 Gly Cys Thr Arg Cys 425 Val Ser Glu Gln Lys 430 Leu Ile
 Ser Glu Glu 435 Asp Leu Gly Gly Gly 440 Pro Arg Lys Pro Thr 445 Thr Thr Pro
 Ala Pro Arg Pro Pro Thr Pro 455 Ala Pro Thr Ile Ala 460 Ser Gln Pro Leu
 Ser Leu Arg Pro Glu Ala 470 Cys Arg Pro Ala Ala 475 Gly Gly Ala Val His 480
 Thr Arg Gly Leu Asp 485 Phe Ala Cys Asp Ile 490 Tyr Ile Trp Ala Pro 495 Leu
 Ala Gly Thr Cys 500 Gly Val Leu Leu Leu 505 Ser Leu Val Ile Thr 510 Lys Arg
 Gly Arg Lys 515 Lys Leu Leu Tyr Ile 520 Phe Lys Gln Pro Phe 525 Met Arg Pro
 Val Gln Thr Thr Gln Glu Glu 535 Asp Gly Cys Ser Cys 540 Arg Phe Pro Glu
 Glu Glu Glu Gly Gly Cys 550 Glu Leu Arg Val Lys 555 Phe Ser Arg Ser Ala 560
 Asp Ala Pro Ala Tyr 565 Gln Gln Gly Gln Asn 570 Gln Leu Tyr Asn Glu 575 Leu
 Asn Leu Gly Arg 580 Arg Glu Glu Tyr Asp 585 Val Leu Asp Lys Arg 590 Arg Gly
 Arg Asp Pro Glu Met Gly Gly Lys 600 Pro Gln Arg Arg Lys 605 Asn Pro Gln
 Glu Gly Leu Tyr Asn Glu Leu Gln Lys Asp Lys Met 620 Ala Glu Ala Tyr
 Ser Glu Ile Gly Met Lys 630 Gly Glu Arg Arg Arg 635 Gly Lys Gly His Asp 640
 Gly Leu Tyr Gln Gly 645 Leu Ser Thr Ala Thr 650 Lys Asp Thr Tyr Asp 655 Ala
 Leu His Met Gln 660 Ala Leu Pro Pro Arg 665

SP102075SGM SEQUENCE LISTING

<211> 706
<212> PRT
<213> Unknown

<220>
<223> HUMAN

<400> 26
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
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Val His Ser Thr Ser Pro Cys Asp Asn Phe Asp Cys Gln Asn Gly Ala
20 25 30
Gln Cys Ile Val Arg Ile Asn Glu Pro Ile Cys Gln Cys Leu Pro Gly
35 40 45
Tyr Gln Gly Glu Lys Cys Glu Lys Leu Val Ser Val Asn Phe Ile Asn
50 55 60
Lys Glu Ser Tyr Leu Gln Ile Pro Ser Ala Lys Val Arg Pro Gln Thr
65 70 75 80
Asn Ile Thr Leu Gln Ile Ala Thr Asp Glu Asp Ser Gly Ile Leu Leu
85 90 95
Tyr Lys Gly Asp Lys Asp His Ile Ala Val Glu Leu Tyr Arg Gly Arg
100 105 110
Val Arg Ala Ser Tyr Asp Thr Gly Ser His Pro Ala Ser Ala Ile Tyr
115 120 125
Ser Val Glu Thr Ile Asn Asp Gly Asn Phe His Ile Val Glu Leu Leu
130 135 140
Ala Leu Asp Gln Ser Leu Ser Leu Ser Val Asp Gly Gly Asn Pro Lys
145 150 155 160
Ile Ile Thr Asn Leu Ser Lys Gln Ser Thr Leu Asn Phe Asp Ser Pro
165 170 175
Leu Tyr Val Gly Gly Met Pro Gly Lys Ser Asn Val Ala Ser Leu Arg
180 185 190
Gln Ala Pro Gly Gln Asn Gly Thr Ser Phe His Gly Cys Ile Arg Asn
195 200 205
Leu Tyr Ile Asn Ser Glu Leu Gln Asp Phe Gln Lys Val Pro Met Gln
210 215 220
Thr Gly Ile Leu Pro Gly Cys Glu Pro Cys His Lys Lys Val Cys Ala
225 230 235 240
His Gly Thr Cys Gln Pro Ser Ser Gln Ala Gly Phe Thr Cys Glu Cys
245 250 255
Gln Glu Gly Trp Met Gly Pro Leu Cys Asp Gln Arg Thr Asn Asp Pro
260 265 270
Cys Leu Gly Asn Lys Cys Val His Gly Thr Cys Leu Pro Ile Asn Ala
275 280 285
Phe Ser Tyr Ser Cys Lys Cys Leu Glu Gly His Gly Gly Val Leu Cys
290 295 300
Asp Glu Glu Glu Asp Leu Phe Asn Pro Cys Gln Ala Ile Lys Cys Lys
305 310 315 320

SP102075SGM SEQUENCE LISTING

His Gly Lys Cys Arg₃₂₅ Leu Ser Gly Leu Gly₃₃₀ Gln Pro Tyr Cys Glu₃₃₅ Cys
 Ser Ser Gly Tyr₃₄₀ Thr Gly Asp Ser Cys₃₄₅ Asp Arg Glu Ile Ser₃₅₀ Cys Arg
 Gly Glu Arg₃₅₅ Ile Arg Asp Tyr Tyr₃₆₀ Gln Lys Gln Gln Gly₃₆₅ Tyr Ala Ala
 Cys Gln Thr Thr Lys Lys Val₃₇₅ Ser Arg Leu Glu Cys₃₈₀ Arg Gly Gly Cys
 Ala Gly Gly Gln Cys Cys₃₉₀ Gly Pro Leu Arg Ser₃₉₅ Lys Arg Arg Lys Tyr₄₀₀
 Ser Phe Glu Cys Thr₄₀₅ Asp Gly Ser Ser Phe Val₄₁₀ Asp Glu Val Glu₄₁₅ Lys
 Val Val Lys Cys₄₂₀ Gly Cys Thr Arg Cys₄₂₅ Val Ser Glu Gln Lys₄₃₀ Leu Ile
 Ser Glu Glu₄₃₅ Asp Leu Gly Gly Gly₄₄₀ Pro Arg Lys Pro Thr₄₄₅ Thr Thr Pro
 Ala Pro Arg Pro Pro Thr Pro₄₅₅ Ala Pro Thr Ile Ala₄₆₀ Ser Gln Pro Leu
 Ser₄₆₅ Leu Arg Pro Glu Ala₄₇₀ Cys Arg Pro Ala Ala₄₇₅ Gly Gly Ala Val His₄₈₀
 Thr Arg Gly Leu Asp₄₈₅ Phe Ala Cys Asp Ile₄₉₀ Tyr Ile Trp Ala Pro₄₉₅ Leu
 Ala Gly Thr Cys₅₀₀ Gly Val Leu Leu Leu₅₀₅ Ser Leu Val Ile Thr₅₁₀ Arg Ser
 Lys Arg Ser₅₁₅ Arg Gly Gly His Ser₅₂₀ Asp Tyr Met Asn Met₅₂₅ Thr Pro Arg
 Arg Pro Gly Pro Thr Arg Lys₅₃₅ His Tyr Gln Pro Tyr₅₄₀ Ala Pro Pro Arg
 Asp₅₄₅ Phe Ala Ala Tyr Arg₅₅₀ Ser Lys Arg Gly Arg₅₅₅ Lys Lys Leu Leu Tyr₅₆₀
 Ile Phe Lys Gln Pro Phe Met Arg Pro Val₅₇₀ Gln Thr Thr Gln Glu₅₇₅ Glu
 Asp Gly Cys Ser₅₈₀ Cys Arg Phe Pro Glu₅₈₅ Glu Glu Glu Gly₅₉₀ Gly Cys Glu
 Leu Arg Val₅₉₅ Lys Phe Ser Arg Ser₆₀₀ Ala Asp Ala Pro Ala₆₀₅ Tyr Gln Gln
 Gly Gln Asn Gln Leu Tyr Asn₆₁₅ Glu Leu Asn Leu Gly₆₂₀ Arg Arg Glu Glu
 Tyr₆₂₅ Asp Val Leu Asp Lys₆₃₀ Arg Arg Gly Arg Asp₆₃₅ Pro Glu Met Gly Gly₆₄₀
 Lys Pro Gln Arg Arg₆₄₅ Lys Asn Pro Gln Glu₆₅₀ Gly Leu Tyr Asn Glu₆₅₅ Leu
 Gln Lys Asp Lys₆₆₀ Met Ala Glu Ala Tyr₆₆₅ Ser Glu Ile Gly Met₆₇₀ Lys Gly
 Glu Arg Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser

SP102075SGM SEQUENCE LISTING															
675					680					685					
Thr	Ala	Thr	Lys	Asp	Thr	Tyr	Asp	Ala	Leu	His	Met	Gln	Ala	Leu	Pro
690						695					700				
Pro	Arg														
705															