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(54) Title: HLA CLASS I-RESTRICTED T CELL RECEPTORS AGAINST RAS WITH G12D MUTATION

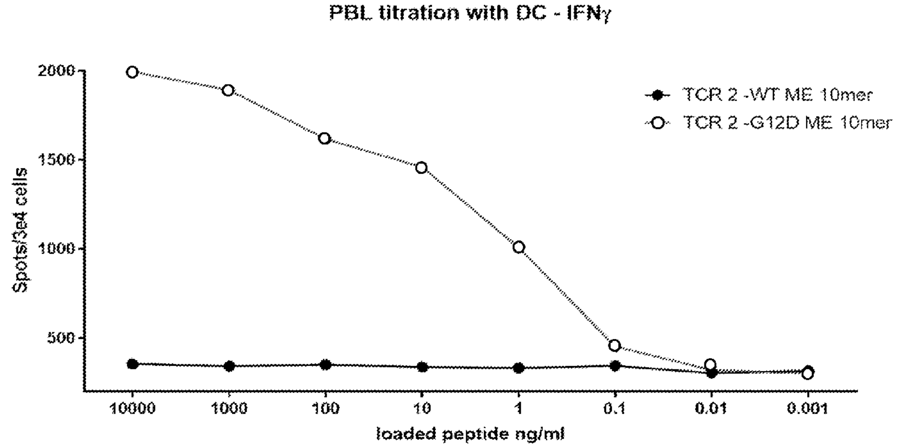

Fig. 4A

(57) **Abstract:** Disclosed is an isolated or purified T cell receptor (TCR), wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid presented by a human leukocyte antigen (HLA) Class I molecule. Related polypeptides and proteins, as well as related nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions are also provided. Also disclosed are methods of detecting the presence of cancer in a mammal and methods of treating or preventing cancer in a mammal.

[Continued on next page]

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HLA CLASS I–RESTRICTED T CELL RECEPTORS AGAINST RAS WITH G12D MUTATION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/975,544, filed February 12, 2020, which is incorporated by reference in its entirety herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under project number ZIABC010984 by the National Institutes of Health, National Cancer Institute. The Government has certain rights in the invention.

INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0003] Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 114,961 Byte ASCII (Text) file named “751506_ST25.txt,” dated January 29, 2021.

BACKGROUND OF THE INVENTION

[0004] Some cancers may have very limited treatment options, particularly when the cancer becomes metastatic and unresectable. Despite advances in treatments such as, for example, surgery, chemotherapy, and radiation therapy, the prognosis for many cancers, such as, for example, pancreatic, colorectal, lung, endometrial, ovarian, and prostate cancers, may be poor. Accordingly, there exists an unmet need for additional treatments for cancer.

BRIEF SUMMARY OF THE INVENTION

[0005] An embodiment of the invention provides an isolated or purified T-cell receptor (TCR) comprising the amino acid sequences of (a) SEQ ID NOs: 1-3, (b) SEQ ID NOs: 4-6, or (c) SEQ ID NOs: 1-6, wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid, presented by a human leukocyte antigen (HLA) Class I molecule, wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS), a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS), or a mutated human Neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence, and wherein position 12 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS protein, respectively.

[0006] Another embodiment of the invention provides an isolated or purified polypeptide comprising a functional portion of the inventive TCR, wherein the functional portion comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, or (c) all of SEQ ID NOs: 1-6.

[0007] Still another embodiment of the invention provides an isolated or purified protein, comprising a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 1-3 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 4-6.

[0008] Embodiments of the invention further provide nucleic acids, recombinant expression vectors, host cells, populations of cells, and pharmaceutical compositions relating to the inventive TCRs, polypeptides, and proteins.

[0009] An embodiment of the invention provides an isolated or purified nucleic acid comprising, from 5’ to 3’, a first nucleic acid sequence and a second nucleotide sequence, wherein the first and second nucleotide sequence, respectively, encode the amino sequences of SEQ ID NOs: 7 and 8; 51 and 8; 7 and 52; 51 and 52; 8 and 7; 8 and 51; 52 and 7; 52 and 51; 21 and 22; 53 and 22; 21 and 54; 53 and 54; 22 and 21; 22 and 53; 54 and 21; 54 and 53; 23 and 24; 55 and 24; 23 and 56; 55 and 56; 24 and 23; 24 and 55; 56 and 23; 56 and 55; 32 and 33; 33 and 32; 59 and 60; 60 and 59; 34 and 35; 35 and 34; 61 and 62; 62 and 61; 36 and 37; 37 and 36; 63 and 64; 64 and 63; 40 and 41; 57 and 41; 40 and 58; 57 and 58; 41 and 40; 41 and 57; 58 and 40; 58 and 57; 42 and 43; 43 and 42; 65 and 66; or 66 and 65.

[0010] Methods of detecting the presence of cancer in a mammal, methods of treating or preventing cancer in a mammal, methods of inducing an immune response against a cancer in a mammal, methods of producing a host cell expressing a TCR that has antigenic specificity for the peptide of VVVGA**D**GVGK (SEQ ID NO: 29), and methods of producing the inventive TCRs, polypeptides, and proteins, are further provided by embodiments of the invention.

[0011] Additional embodiments are as described herein.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S)

[0012] Figures 1A-1B: TIL screening for reactivity to KRAS G12D. Fig. 1A is a graph showing ELISPOT measurement of IFN-γ secretion (number of spots per 3e4 cells). Fig. 1B is a graph showing the flow cytometry assay results of 4-1BB and OX40 (% 4-1BB+/OX40+) expression measured following co-culture of effector cells with target cells. The effector cells were TIL from Patient 4373's tumor fragments F4, F5, F6, F8, F9, and F10. The target cells (autologous DC) were mRNA electroporated with a tandem minigene (TMG) encoding 12 RAS mutations (G12D- G12V- G12C- G12A- G12S-G13D- G13R- G13V-Q61R- Q61L- Q61K- Q61H) (SEQ ID NO: 49) (open circles), or to the wild-type (WT) RAS epitopes (WT G12+G13+Q61) sequence (SEQ ID NO: 48) (shaded circles); autologous DC loaded with G12 WT long peptide (LP) (MTEYKLVVVGA**G**GVGKSALTIQLI) (SEQ ID NO: 27) (shaded squares); G12D Mut LP (MTEYKLVVVGA**D**GVGKSALTIQLI) (SEQ ID NO: 26) (open squares); or minimal epitope (ME) A11/A02 - mix of equal concentration of three peptide sequences: KLVVVGADGV (SEQ ID NO: 50), VVGADGVGK (SEQ ID NO: 28), VVVGADGVGK (SEQ ID NO: 29) (shaded triangles). As negative controls, the autologous DC cells were cultured alone (TIL only) (diamonds) or co-cultured with: dimethyl sulfoxide (DMSO) (open triangles). As a positive control, TIL grows in the presence of anti-CD3/anti-CD28 Dynabeads (ThermoFisher) material (stars).

[0013] Figure 2 is a graph showing the percentage of cells expressing 4-1BB and OX40 following co-culture of effector cells with target cells. The effector cells were Patient 4373's autologous PBL transduced with (i) one of two TCRs sequences (TCR1 or TCR2) obtained by a single-cell sequencing method from the reactive TILs (shown in Figure 1) that were suspected as being G12D RAS-reactive or (ii) the HLA-A11 restricted, murine anti-KRAS

G12D TCR (positive control) (mTCR) or (iii) not transduced PBL (-). The target cells were: COS HLA-A2 cell line (open circles), COS HLA-A2-G12D cell line (closed circles), COS HLA-A11 cell line (open triangles), or COS HLA-A11-G12D cell line (closed triangles), or T cell only (without target cells) (-).

[0014] Figures 3A-3B: 4373 TCR transduced PBLs tested for reactivity to KRAS G12D. Fig. 3A is graph showing the ELISPOT measurement of IFN-γ secretion (number of spots per 3e4 cells). Fig. 3B is a graph showing the flow cytometry assay results of 4-1BB and OX40 (% 4-1BB+/OX40+) expression of CD8 gated cells measured following co-culture of effector cells with target cells. The effector cells were Patient 4373's autologous CD8+ PBL transduced with the retroviral expression vector encoding (i) the 4373 TCR 1 and 2 suspected as G12D RAS-reactive (with human variable regions); (ii) the HLA-A11 restricted, murine anti-KRAS G12D TCR of Example 1; or (iii) green fluorescent protein (GFP) (control). Cells transduced with an empty vector served as an additional control (Mock Td). The target cells were autologous dendritic cells (DC) mRNA transfected with full length (FL) that has been ether WT KRAS gene (open circles), or FL KRAS G12D mutation gene (closed circles); autologous DC loaded with peptide that has been WT KRAS LP (open triangle) or, G12D Mut KRAS LP (closed triangles) or loaded with KRAS minimal epitope (ME): ME A02 WT (open diamonds); ME A02 G12D (closed diamonds); ME HLA-A11 WT mix (open squares); or ME HLA-A11 G12D mix (closed squares). As a control, the transduced cells were cultured alone (T cells only) (asterisks) or cultured with DMSO (stars) or anti-CD28/anti-CD3 Dynabeads material (hexagons).

[0015] Figures 4A-4C: TCR Avidity test against autologous DC loaded with titration of ME: Fig. 4A is a graph showing ELISPOT IFN-γ secretion results (number of spots per 3e4 cells). Figs. 4B. and 4C are graphs showing the flow cytometry assay results of 4-1BB and OX40 (% 4-1BB+/OX40+) expression (4B) for CD8 gated and for CD4 gated mTCR positive PBL (4C). measured following co-culture of effector cells with target cells. The effector cells were Patient 4373's autologous PBL transduced with a retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions). The target cells were Patient 4373's autologous DCs loaded with the following peptides at the concentrations shown: a mutated minimal epitope peptide with 10 amino acid residues

(VVVGA**D**GVGK) (SEQ ID NO: 29) (open circles) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31) (closed circles).

[0016] Figures 5A-5C: TCR Avidity test against autologous COS-A11 cell line loaded with titration of ME: Fig. 5A is a graph showing ELISPOT IFN-γ secretion results (number of spots per 3e4 cells). Figs. 5B and 5C are graphs showing flow cytometry assay results of 4-1BB and OX40 (% 4-1BB+/OX40+) expression for CD8 gated (5B) and for CD4 gated mTCR positive PBL (5C) measured following co-culture of effector cells with target cells. The effector cells were Patient 4373's autologous PBL transduced with a retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions). The target cells were Patient 4373's autologous DCs loaded with the following peptides at the concentrations shown: a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29) (open circles) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31) (closed circles).

DETAILED DESCRIPTION OF THE INVENTION

[0017] RAS family proteins belong to the large family of small GTPases. Without being bound to a particular theory or mechanism, it is believed that, when mutated, RAS proteins may be involved in signal transduction early in the oncogenesis of many human cancers. A single amino acid substitution may activate the protein. The mutated RAS protein product may be constitutively activated. Mutated RAS proteins may be expressed in any of a variety of human cancers such as, for example, pancreatic (e.g., pancreatic carcinoma), colorectal, lung (e.g., lung adenocarcinoma), endometrial, ovarian (e.g., epithelial ovarian cancer), and prostate cancers. The human RAS family proteins include KRAS, HRAS, and NRAS.

[0018] KRAS is also referred to as GTPase KRas, V-Ki-Ras2 Kirsten rat sarcoma viral oncogene, or KRAS2. There are two transcript variants of KRAS: KRAS variant A and KRAS variant B. Wild-type (WT) KRAS variant A has the amino acid sequence of SEQ ID NO: 9. WT KRAS variant B has the amino acid sequence of SEQ ID NO: 10. Hereinafter, references to "KRAS" (mutated or unmutated (WT)) refer to both variant A and variant B, unless specified otherwise. When activated, mutated KRAS binds to guanosine-5'-triphosphate (GTP) and converts GTP to guanosine 5′-diphosphate (GDP).

[0019] HRAS is another member of the RAS protein family. HRAS is also referred to as Harvey Rat Sarcoma Viral Oncoprotein, V-Ha-Ras Harvey Rat Sarcoma Viral Oncogene Homolog, or Ras Family Small GTP Binding Protein H-Ras. WT HRAS has the amino acid sequence of SEQ ID NO: 11.

[0020] NRAS is still another member of the RAS protein family. NRAS is also referred to as GTPase NRas, V-Ras Neuroblastoma RAS Viral Oncogene Homolog, or NRAS1. WT NRAS has the amino acid sequence of SEQ ID NO: 12.

[0021] An embodiment of the invention provides an isolated or purified TCR, wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid, wherein the mutated human RAS amino acid sequence is a mutated human KRAS, a mutated human HRAS, or a mutated human NRAS amino acid sequence, and wherein position 12 is defined by reference to the WT human KRAS, WT human HRAS, or WT human NRAS protein, respectively. Hereinafter, references to a “TCR” also refer to functional portions and functional variants of the TCR, unless specified otherwise.

[0022] The mutated human RAS amino acid sequence may be a mutated human KRAS amino acid sequence, a mutated human HRAS amino acid sequence, or a mutated human NRAS amino acid sequence. The amino acid sequences of WT human KRAS, NRAS, and HRAS protein each have a length of 188 or 189 amino acid residues and have a high degree of identity to one another. For example, the amino acid sequence of the WT human NRAS protein is 86.8% identical to that of the WT human KRAS protein. Amino acid residues 1-86 of the WT human NRAS protein and the WT human KRAS protein are 100% identical. The amino acid sequence of the WT human HRAS protein is 86.3% identical to that of the WT human KRAS protein. Amino acid residues 1-94 of the WT human HRAS protein and the WT human KRAS protein are 100% identical. Hereinafter, references to “RAS” (mutated or unmutated (WT)) collectively refer to KRAS, HRAS, and NRAS, unless specified otherwise.

[0023] In an embodiment of the invention, the mutated human RAS amino acid sequence comprises a human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid, wherein position 12 is defined by reference to the corresponding WT RAS protein. The WT RAS protein may be any one of WT KRAS protein (SEQ ID NO: 9 or 10), WT HRAS protein (SEQ ID NO: 11), or WT NRAS protein (SEQ ID NO: 12) because, as explained above, amino acid residues 1-86 of the WT human NRAS protein and the WT human KRAS protein are 100% identical, and amino acid residues 1-94 of the WT human HRAS protein and the WT human KRAS protein are 100% identical. Accordingly, the amino acid residue at position 12 of each of WT KRAS, WT HRAS, and WT NRAS protein is the same, namely, glycine.

[0024] The mutated human RAS amino acid sequence has a substitution of glycine at position 12 with aspartic acid. In this regard, embodiments of the invention provide TCRs with antigenic specificity for any human RAS protein, polypeptide or peptide amino acid sequence with a G12D mutation.

[0025] Mutations and substitutions of RAS are defined herein by reference to the amino acid sequence of the corresponding WT RAS protein. Thus, mutations and substitutions of RAS are described herein by reference to the amino acid residue present at a particular position in WT RAS protein (namely, position 12), followed by the position number, followed by the amino acid residue with which that residue has been replaced in the particular mutation or substitution under discussion. A RAS amino acid sequence (e.g., a RAS peptide) may comprise fewer than all of the amino acid residues of the full-length, WT RAS protein. Accordingly, position 12 is defined herein by reference to the WT full-length RAS protein (namely, any one of SEQ ID NOs: 9-12) with the understanding that the actual position of the corresponding residue in a particular example of a RAS amino acid sequence may be different. When the positions are as defined by any one of SEQ ID NOs: 9-12, the term "G12" refers to the glycine normally present at position 12 of any one of SEQ ID NOs: 9-12, and "G12D" indicates that the glycine normally present at position 12 of any one of SEQ ID NOs: 9-12 is replaced by aspartic acid. For example, when a particular example of a RAS amino acid sequence is, e.g., VVVGA<u>G</u>GVGK (SEQ ID NO: 31) (an exemplary WT KRAS peptide corresponding to contiguous amino acid residues 7 to 16 of SEQ ID NO: 9), "G12D" refers to a substitution of the underlined glycine in SEQ ID NO: 31 with aspartic acid, even though the actual position of the underlined glycine in SEQ ID NO: 31 is 6. Human RAS amino acid sequences with the G12D mutation are hereinafter referred to as "G12D RAS".

[0026] Examples of full-length RAS proteins with the G12D mutation are set forth in Table 1 below.

TABLE 1

Mutated Full-Length RAS Protein	**SEQ ID NO:**
G12D KRAS variant A	13
G12D KRAS variant B	14
G12D HRAS	15
G12D NRAS	16

[0027] In an embodiment of the invention, the TCR has antigenic specificity for a RAS peptide with the G12D mutation described above, wherein the G12D RAS peptide has any length. In an embodiment of the invention, the G12D RAS peptide has any length suitable for binding to any of the HLA Class I molecules described herein. For example, the TCR may have antigenic specificity for a RAS peptide with the G12D mutation, the RAS peptide having a length of about 9 to about 10 amino acid residues. The G12D RAS peptide may comprise any contiguous amino acid residues of mutated RAS protein which include the G12D mutation. In an embodiment of the invention, the TCR may have antigenic specificity for a RAS peptide with the G12D mutation, the mutated RAS peptide having a length of about 9 amino acid residues or about 10 amino acid residues. Examples of specific peptides, each with the G12D mutation, which may be recognized by the inventive TCR are 9-mer VVGA**D**GVGK (SEQ ID NO: 28) and 10-mer VVVGA**D**GVGK (SEQ ID NO: 29). In an embodiment of the invention, the TCR has antigenic specificity for the mutated human RAS amino acid sequence of SEQ ID NO: 29. In an embodiment of the invention, the TCR does not have antigenic specificity for the wild-type human RAS amino acid sequence of VVGA**G**GVGK (SEQ ID NO: 30) or 10-mer VVVGA**G**GVGK (SEQ ID NO: 31).

[0028] In an embodiment of the invention, the inventive TCRs are able to recognize G12D RAS presented by an HLA Class I molecule. In this regard, the TCR may elicit an immune response upon binding to G12D RAS within the context of an HLA Class I molecule. The inventive TCRs are able to recognize G12D RAS that is presented by an HLA Class I molecule and may bind to the HLA Class I molecule in addition to G12D RAS.

[0029] In an embodiment of the invention, the HLA Class I molecule is an HLA-A molecule. The HLA-A molecule is a heterodimer of an α chain and β2 microglobulin. The HLA-A α chain may be encoded by an HLA-A gene. β2 microglobulin binds non-covalently to the α1, α2 and α3 domains of the α chain to build the HLA-A complex. The HLA-A molecule may be any HLA-A molecule. In an embodiment of the invention, the HLA Class I molecule is an HLA-A11 molecule. The HLA-A11 molecule may be any HLA-A11 molecule. Examples of HLA-A11 molecules may include, but are not limited to, those encoded by the HLA-A*11:01, HLA-A*11:02, HLA-A*11:03, or HLA-A*11:04 alleles. Preferably, the HLA Class I molecule is encoded by the HLA-A*11:01 allele.

[0030] The TCRs of the invention may provide any one or more of a variety of advantages, including when expressed by cells used for adoptive cell transfer. G12D RAS is expressed by cancer cells and is not expressed by normal, noncancerous cells. Without being bound to a particular theory or mechanism, it is believed that the inventive TCRs advantageously target the destruction of cancer cells while minimizing or eliminating the destruction of normal, non-cancerous cells, thereby reducing toxicity. Moreover, because the G12D mutation is likely to occur in the early stages of tumorigenesis, the G12D RAS mutation may be expressed on substantially all of a patient's cancer cells. The inventive TCRs may, advantageously, successfully treat or prevent G12D RAS-positive cancers that do not respond to other types of treatment such as, for example, chemotherapy, surgery, or radiation. Additionally, the inventive TCRs may provide highly avid recognition of G12D RAS, which may provide the ability to recognize unmanipulated tumor cells (e.g., tumor cells that have not been treated with interferon (IFN)-γ, transfected with a vector encoding one or both of G12D RAS and HLA-A*11:01, pulsed with a G12D RAS peptide, or a combination thereof). KRAS mutations are found in about 70% of pancreatic cancer, 36% of colorectal cancer and 20% of lung cancer. Most commonly, mutations occur in codon 12 (encoding glycine, G). The KRAS G12D mutation is found in about 36% and about 12% of patients with pancreatic and colorectal cancers, respectively. Moreover, the HLA-A*11:01 allele is expressed in approximately 14% and approximately 9% of the Caucasian and Hispanic ethnicities, respectively. The HLA-A*11:01 allele is expressed by up to about 45% of the Asian ethnicity in the United States. Accordingly, the inventive TCRs may increase the number of immunotherapy-eligible cancer patients to include those patients that express the HLA-A*11:01 allele who may not be eligible for immunotherapy using TCRs that recognize RAS presented by other MHC molecules. Moreover, the inventive TCRs, polypeptides and proteins comprise human complementarity determining region (CDR) and variable region amino acid sequences, which may reduce the risk of rejection by the human immune system as compared to, e.g., TCRs, polypeptides and proteins comprising mouse CDR and variable region amino acid sequences.

[0031] The phrase “antigenic specificity,” as used herein, means that the TCR can specifically bind to and immunologically recognize G12D RAS with high avidity. For example, a TCR may be considered to have “antigenic specificity” for G12D RAS if about 1 x 10^4 to about 1 x 10^5 T cells expressing the TCR secrete at least about 200 pg/mL or more (e.g., 200 pg/mL or more, 300 pg/mL or more, 400 pg/mL or more, 500 pg/mL or more, 600 pg/mL or more, 700 pg/mL or more, 1000 pg/mL or more, 5,000 pg/mL or more, 7,000 pg/mL or more, 10,000 pg/mL or more, 20,000 pg/mL or more, or a range defined by any two of the foregoing values) of IFN-γ upon co-culture with (a) antigen-negative, HLA Class I molecule positive target cells pulsed with a low concentration of G12D RAS peptide (e.g., about 0.05 ng/mL to about 10 ng/mL, 1 ng/mL, 2 ng/mL, 5 ng/mL, 8 ng/mL, 10 ng/mL, or a range defined by any two of the foregoing values) or (b) antigen-negative, HLA Class I molecule positive target cells into which a nucleotide sequence encoding G12D RAS has been introduced such that the target cell expresses G12D RAS. Cells expressing the inventive TCRs may also secrete IFN-γ upon co-culture with antigen-negative, HLA Class I molecule positive target cells pulsed with higher concentrations of G12D RAS peptide. The HLA Class I molecule may be any of the HLA Class I molecules described herein (e.g., an HLA-A*11:01 molecule).

[0032] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for G12D RAS if T cells expressing the TCR secrete at least twice (e.g., five times) as much IFN-γ upon co-culture with (a) antigen-negative, HLA Class I molecule positive target cells pulsed with a low concentration of G12D RAS peptide or (b) antigen-negative, HLA Class I molecule positive target cells into which a nucleotide sequence encoding G12D RAS has been introduced such that the target cell expresses G12D RAS as compared to the amount of IFN-γ expressed by a negative control. The negative control may be, for example, (i) T cells expressing the TCR, co-cultured with (a) antigen-negative, HLA Class I molecule positive target cells pulsed with the same concentration of an irrelevant peptide (e.g., some other peptide with a different sequence from the G12D RAS peptide) or (b) antigen-negative, HLA Class I molecule positive target cells into which a nucleotide sequence encoding an irrelevant peptide has been introduced such that the target cell expresses the irrelevant peptide, or (ii) untransduced T cells (e.g., derived from PBMC, which do not express the TCR) co-cultured with (a) antigen-negative, HLA Class I molecule positive target cells pulsed with the same concentration of G12D RAS peptide or (b) antigen-negative, HLA Class I molecule positive target cells into which a nucleotide sequence encoding G12D RAS has been introduced such that the target cell expresses G12D RAS. The HLA Class I molecule expressed by the target cells of the negative control would be the same HLA Class I molecule expressed by the target cells that are co-cultured with the T cells being tested. The HLA Class I molecule may be any of the HLA Class I molecules described herein (e.g., an HLA-A*11:01 molecule). IFN-γ secretion may be measured by methods known in the art such as, for example, enzyme-linked immunosorbent assay (ELISA).

[0033] Alternatively or additionally, a TCR may be considered to have "antigenic specificity" for G12D RAS if at least twice (e.g., five times) as many of the numbers of T cells expressing the TCR secrete IFN-γ upon co-culture with (a) antigen-negative, HLA Class I molecule positive target cells pulsed with a low concentration of G12D RAS peptide or (b) antigen-negative, HLA Class I molecule positive target cells into which a nucleotide sequence encoding G12D RAS has been introduced such that the target cell expresses G12D RAS as compared to the numbers of negative control T cells that secrete IFN-γ. The HLA Class I molecule, concentration of peptide, and the negative control may be as described herein with respect to other aspects of the invention. The numbers of cells secreting IFN-γ may be measured by methods known in the art such as, for example, ELISPOT.

[0034] Alternatively or additionally, a TCR may be considered to have "antigenic specificity" for G12D RAS if T cells expressing the TCR upregulate expression of one or more T-cell activation markers as measured by, for example, flow cytometry after stimulation with target cells expressing G12D RAS. Examples of T-cell activation markers include 4-1BB, OX40, CD107a, CD69, and cytokines that are upregulated upon antigen stimulation (e.g., tumor necrosis factor (TNF), interleukin (IL)-2, etc.).

[0035] An embodiment of the invention provides a TCR comprising two polypeptides (i.e., polypeptide chains), such as an alpha (α) chain of a TCR, a beta (β) chain of a TCR, a gamma (γ) chain of a TCR, a delta (δ) chain of a TCR, or a combination thereof. The polypeptides of the inventive TCR can comprise any amino acid sequence, provided that the

TCR has antigenic specificity for G12D RAS. In some embodiments, the TCR is non-naturally occurring.

[0036] In an embodiment of the invention, the TCR comprises two polypeptide chains, each of which comprises a variable region comprising a complementarity determining region (CDR)1, a CDR2, and a CDR3 of a TCR. In an embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 1 (CDR1 of α chain of 4373 TCR), a CDR2 comprising the amino acid sequence of SEQ ID NO: 2 (CDR2 of α chain of 4373 TCR), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3 (CDR3 of α chain of 4373 TCR), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 4 (CDR1 of β chain of 4373 TCR), a CDR2 comprising the amino acid sequence of SEQ ID NO: 5 (CDR2 of β chain of 4373 TCR), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6 (CDR3 of β chain of 4373 TCR).

[0037] In this regard, the inventive TCR can comprise any one or more of the amino acid sequences selected from any of SEQ ID NOs: 1-6. In an embodiment of the invention, the TCR comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, or (c) all of SEQ ID NOs: 1-6. In an especially preferred embodiment, the TCR comprises the amino acid sequences of all of SEQ ID NOs: 1-6.

[0038] The CDR3 of SEQ ID NOs: 3 or 6, i.e., of the α chain or β chain or both, may further comprise a cysteine immediately N-terminal to the first amino acid of the CDR or a phenylalanine immediately C-terminal to the final amino acid or both.

[0039] In an embodiment of the invention, the TCR comprises an amino acid sequence of a variable region of a TCR comprising the CDRs set forth above. In this regard, the TCR can, e.g., comprise the amino acid sequence of: SEQ ID NO: 7 (variable region of α chain of 4373 TCR with wild type N-terminal signal peptide); SEQ ID NO: 51 (variable region of α chain of 4373 TCR with variant N-terminal signal peptide); SEQ ID NO: 8 (variable region of β chain of 4373 TCR with variant N-terminal signal peptide); SEQ ID NO: 52 (variable region of β chain of 4373 TCR with wild type N-terminal signal peptide); SEQ ID NO: 32 (variable region of α chain of 4373 TCR without N-terminal signal peptide predicted with IMGT); SEQ ID NO: 33 (variable region of β chain of 4373 TCR without N-terminal signal peptide predicted with IMGT); SEQ ID NO: 59 (variable region of α chain of 4373 TCR without N-terminal signal peptide predicted with SignalP); SEQ ID NO: 60 (variable region of β chain of 4373 TCR without N-terminal signal peptide predicted with SignalP); both of SEQ ID NOs: 7 and 8; both of SEQ ID NOs: 7 and 52; both of SEQ ID NOs: 51 and 8; both of SEQ ID NOs: 51 and 52; both of SEQ ID NOs: 32 and 33 or both of SEQ ID NOs: 59 and 60. Preferably, the TCR comprises the amino acid sequences of (i) both of SEQ ID NOs: 7 and 8, (ii) both of SEQ ID NOs: 51 and 52 or (iii) both of SEQ ID NOs: 32 and 33.

[0040] The inventive TCRs may further comprise an α chain constant region and a β chain constant region. The constant region may be derived from any suitable species such as, e.g., human or mouse. In an embodiment of the invention, the TCRs further comprise murine α and β chain constant regions or human α and β chain constant regions. As used herein, the term "murine" or "human," when referring to a TCR or any component of a TCR described herein (e.g., CDR, variable region, constant region, α chain, and/or β chain), means a TCR (or component thereof) which is derived from a mouse or a human, respectively, i.e., a TCR (or component thereof) that originated from or was, at one time, expressed by a mouse T cell or a human T cell, respectively.

[0041] An embodiment of the invention provides a chimeric TCR comprising a human variable region and a murine constant region, wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid, presented by an HLA Class I molecule. The murine constant region may provide any one or more advantages. For example, the murine constant region may diminish mispairing of the inventive TCR with endogenous TCRs of the host cell into which the inventive TCR is introduced. Alternatively or additionally, the murine constant region may increase expression of the inventive TCR as compared to the same TCR with a human constant region. The chimeric TCR may comprise the amino acid sequence of SEQ ID NO: 19 (WT murine α chain constant region), SEQ ID NO: 20 (WT murine β chain constant region), or both SEQ ID NOs: 19 and 20. Preferably, the inventive TCR comprises the amino acid sequences of both of SEQ ID NOs: 19 and 20. The chimeric TCR may comprise any of the murine constant regions described herein in combination with any of the CDR regions as described herein with respect to other aspects of the invention. In this regard, the TCR, e.g., may comprise the amino acid sequences of: (a) all of SEQ ID NOs: 1-3 and 19; (b) all of SEQ ID NOs: 4-6 and 20; or (c) all of SEQ ID NOs: 1-6 and 19-20. In another embodiment of the invention, the chimeric TCR may comprise any of the murine constant regions described herein in combination with any of the variable regions described herein with respect to other aspects of the invention. In this regard, the TCR, e.g., may comprise the amino acid sequences of: (i) both of SEQ ID NOs: 7 and 19; (ii) both of SEQ ID NOs: 51 and 19; (iii) both of SEQ ID NOs: 8 and 20; (iv) both of SEQ ID NOs: 52 and 20; (v) all of SEQ ID NOs: 7-8 and 19-20, or (iv) all of SEQ ID NOs: 51-52 and 19-20.

[0042] In an embodiment of the invention, the TCR comprises an α chain comprising a variable region and a constant region and a β chain comprising a variable region and a constant region. In this regard, the TCR, e.g., may comprise (a) an α chain comprising the amino acid sequence of SEQ ID NO: 21 (α chain of 4373 TCR with a wild type N-terminal signal peptide), wherein: (i) X at position 193 of SEQ ID NO: 21 is Thr or Cys; (ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (b) an α chain comprising the amino acid sequence of SEQ ID NO: 53 (α chain of 4373 TCR with a variant N-terminal signal peptide), wherein: (i) X at position 193 of SEQ ID NO: 53 is Thr or Cys; (ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (c) a β chain comprising the amino acid sequence of SEQ ID NO: 22 (β chain of 4373 TCR with a variant N-terminal signal peptide), wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys; (d) a β chain comprising the amino acid sequence of SEQ ID NO: 54 (β chain of 4373 TCR with a wild type N-terminal signal peptide), wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys; (e) both (a) and (c), (a) and (d), (b) and (c) or (b) and (d); (f) an α chain comprising the amino acid sequence of SEQ ID NO: 34 (α chain of 4373 TCR without N-terminal signal peptide predicted with IMGT), wherein: (i) X at position 165 of SEQ ID NO: 34 is Thr or Cys; (ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (g) a β chain comprising the amino acid sequence of SEQ ID NO: 35 (β chain of 4373 TCR without N-terminal signal peptide predicted with IMGT), wherein X at position 172 of

SEQ ID NO: 35 is Ser or Cys; (h) an α chain comprising the amino acid sequence of SEQ ID NO: 61 (α chain of 4373 TCR without N-terminal signal peptide predicted with SignalP), wherein: (i) X at position 172 of SEQ ID NO: 61 is Thr or Cys; (ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (i) a β chain comprising the amino acid sequence of SEQ ID NO: 62 (β chain of 4373 TCR without N-terminal signal peptide predicted with SignalP), wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;or (j) both (f) and (g) or both (h) and (i).

[0043] In another embodiment of the invention, the TCR comprises the amino acid sequence(s) of: SEQ ID NO: 23 (4373 TCR α chain with WT murine constant region and WT N-terminal signal peptide), SEQ ID NO: 55 (4373 TCR α chain wild type murine constant region and variant N-terminal signal peptide), SEQ ID NO: 24 (4373 TCR β chain with wild type murine constant region and variant N-terminal signal peptide), SEQ ID NO: 56 (4373 TCR β chain with WT murine constant region and wild type N-terminal signal peptide), SEQ ID NO: 36 (4373 TCR α chain with WT murine constant region and without N-terminal signal peptide predicted with IMGT), SEQ ID NO: 37 (4373 TCR β chain with WT murine constant region and without N-terminal signal peptide predicted with IMGT), SEQ ID NO: 63 (4373 TCR α chain with WT murine constant region and without N-terminal signal peptide predicted with SignalP), SEQ ID NO: 64 (4373 TCR β chain with WT murine constant region and without N-terminal signal peptide predicted with SignalP), both of SEQ ID NOs: 23 and 24, both of SEQ ID NOs: 55 and 24, both of SEQ ID NOs: 23 and 56, both of SEQ ID NOs: 55 and 56, both of SEQ ID NOs: 36 and 37 or both of SEQ ID NOs: 63 and 64.

[0044] In an embodiment of the invention, the TCR comprises a substituted constant region. In this regard, the TCR, e.g., may comprise the amino acid sequence of any of the TCRs described herein with one, two, three, or four amino acid substitution(s) in the constant region of one or both of the α and β chain. Preferably, the TCR comprises a murine constant region with one, two, three, or four amino acid substitution(s) in the murine constant region of one or both of the α and β chains. In an especially preferred embodiment, the TCR comprises a murine constant region with one, two, three, or four amino acid substitution(s) in the murine constant region of the α chain and one amino acid substitution in the murine constant region of the β chain. In some embodiments, the TCRs comprising the substituted constant region advantageously provide one or more of increased recognition of G12D RAS$^+$ targets, increased expression by a host cell, diminished mispairing with endogenous TCRs, and increased anti-tumor activity as compared to the parent TCR comprising an unsubstituted (wild-type) constant region. In general, the substituted amino acid sequences of the murine constant regions of the TCR α and β chains, SEQ ID NOs: 17 and 18, respectively, correspond with all or portions of the unsubstituted murine constant region amino acid sequences SEQ ID NOs: 19 and 20, respectively, with SEQ ID NO: 17 having one, two, three, or four amino acid substitution(s) when compared to SEQ ID NO: 19 and SEQ ID NO: 18 having one amino acid substitution when compared to SEQ ID NO: 20. In this regard, an embodiment of the invention provides a TCR comprising the amino acid sequences of (a) SEQ ID NO: 17 (constant region of α chain), wherein (i) X at position 48 is Thr or Cys; (ii) X at position 112 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 114 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 115 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (b) SEQ ID NO: 18 (constant region of β chain), wherein X at position 57 is Ser or Cys; or (c) both of SEQ ID NOs: 17 and 18. In an embodiment of the invention, the TCR comprising SEQ ID NO: 17 does not comprise SEQ ID NO: 19 (unsubstituted murine constant region of α chain). In an embodiment of the invention, the TCR comprising SEQ ID NO: 18 does not comprise SEQ ID NO: 20 (unsubstituted murine constant region of β chain).

[0045] The first amino acid of any of the mouse alpha constant regions described herein may be different from N as provided in SEQ ID NOS: 17 and 19. For example, in any TCR construct, polypeptide, protein, etc., as described herein, this first amino acid can be encoded by a split codon (having nucleotides from both a variable region and a constant region) such that any of the murine alpha constant regions may have a different amino acid at that position. Similarly, the first amino acid of any of the mouse beta constant regions described herein may be different from E as provided in SEQ ID NOS: 18 and 20, e.g., this first amino acid can be encoded by a split codon.

[0046] In an embodiment of the invention, the substituted constant region includes cysteine substitutions in the constant region of one or both of the α and β chains to provide a cysteine-substituted TCR. Opposing cysteines in the α and the β chains provide a disulfide bond that links the constant regions of the α and the β chains of the substituted TCR to one another and which is not present in a TCR comprising the unsubstituted murine constant regions. In this regard, the TCR, e.g., may be a cysteine-substituted TCR in which one or both of the native Thr at position 48 (Thr48) of SEQ ID NO: 19 and the native Ser at position 57 (Ser57) of SEQ ID NO: 20 may be substituted with Cys. Preferably, both of the native Thr48 of SEQ ID NO: 19 and the native Ser57 of SEQ ID NO: 20 are substituted with Cys. Examples of cysteine-substituted TCR constant regions sequences are set forth in Table 2. In an embodiment of the invention, the cysteine-substituted TCR comprises (i) SEQ ID NO: 17, (ii) SEQ ID NO: 18, or (iii) both of SEQ ID NOs: 17 and 18, wherein both of SEQ ID NOs: 17 and 18 are as defined in Table 2. The cysteine-substituted TCRs of the invention may include the substituted constant region in addition to any of the CDRs or variable regions described herein.

[0047] In an embodiment of the invention, the cysteine-substituted, chimeric TCR comprises a full length α chain and a full-length β chain. Examples of cysteine-substituted, chimeric TCR α chain and β chain sequences are set forth in Table 2. In an embodiment of the invention, the TCR comprises (i) SEQ ID NO: 21, (ii) SEQ ID NO: 53, (iii) SEQ ID NO: 22, (iv) SEQ ID NO: 54, (v) SEQ ID NO: 34, (vi) SEQ ID NO: 35, (vii) SEQ ID NO: 61, (viii) SEQ ID NO: 62, (ix) both of SEQ ID NO: 21 and 22, (x) both of SEQ ID NOs: 53 and 22, (xi) both of SEQ ID NOs: 21 and 54, (xii) both of SEQ ID NOs: 53 and 54, (xiii) both of SEQ ID NOs: 34 and 35, or (xiv) both of SEQ ID NOs: 61 and 62, wherein all of SEQ ID NOs: 21-22, 34-35, 53, 54, 61 and 62 are as defined in Table 2.

TABLE 2

SEQ ID NO:	**Definitions of "X" in some embodiments**
SEQ ID NO: 17 (constant region α chain)	X at position 48 is Cys, X at position 112 is Ser, X at position 114 is Met, and X at position 115 is Gly.
SEQ ID NO: 18 (constant region β chain)	X at position 57 is Cys
SEQ ID NO: 21	X at position 193 is Cys,

SEQ ID NO:	Definitions of "X" in some embodiments
(4373 TCR α chain) (with wild type N-terminal signal peptide)	X at position 257 is Ser, X at position 259 is Met, and X at position 260 is Gly.
SEQ ID NO: 22 (4373 TCR β chain) (with variant N-terminal signal peptide)	X at position 191 is Cys
SEQ ID NO: 34 (4373 TCR α chain) (predicted sequence using IMGT without N-terminal signal peptide)	X at position 165 is Cys, X at position 229 is Ser, X at position 231 is Met, and X at position 232 is Gly.
SEQ ID NO: 35 (4373 TCR β chain) (predicted sequence using IMGT without N-terminal signal peptide)	X at position 172 is Cys
SEQ ID NO: 53 (4373 TCR α chain) (with variant N-terminal signal peptide)	X at position 193 is Cys, X at position 257 is Ser, X at position 259 is Met, and X at position 260 is Gly.
SEQ ID NO: 54 (4373 TCR β chain) (with wild type N-terminal signal peptide)	X at position 191 is Cys
SEQ ID NO: 61	X at position 172 is Cys, X at position 236 is Ser, X at position 238 is Met, and

SEQ ID NO:	Definitions of "X" in some embodiments
(4373 TCR α chain) (predicted sequence using SignalP without N-terminal signal peptide)	X at position 239 is Gly.
SEQ ID NO: 62 (4373 TCR β chain) (predicted sequence using SignalP without N-terminal signal peptide)	X at position 170 is Cys

[0048] In an embodiment of the invention, the substituted amino acid sequence includes substitutions of one, two, or three amino acids in the transmembrane (TM) domain of the constant region of the α chain with a hydrophobic amino acid to provide a hydrophobic amino acid-substituted TCR (also referred to herein as an "LVL-modified TCR"). The hydrophobic amino acid substitution(s) in the TM domain of the TCR may increase the hydrophobicity of the TM domain of the TCR as compared to a TCR that lacks the hydrophobic amino acid substitution(s) in the TM domain. In this regard, the TCR is an LVL-modified TCR in which one, two, or three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 19 may, independently, be substituted with Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably with Leu, Ile, or Val; and the native Ser57 of SEQ ID NO: 20 may be substituted with Cys . Preferably, all three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 19 may, independently, be substituted with Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably with Leu, Ile, or Val. In an embodiment of the invention, the LVL-modified TCR comprises (i) SEQ ID NO: 17, (ii) SEQ ID NO: 18, or (iii) both of SEQ ID NOs: 17 and 18, wherein both of SEQ ID NOs: 17 and 18 are as defined in Table 3. The LVL-modified TCRs of the invention may include the substituted constant region in addition to any of the CDRs or variable regions described herein.

[0049] In an embodiment of the invention, the LVL-modified TCR comprises a full length α chain and a full-length β chain. Examples of LVL-modified TCR α chain and β chain sequences are set forth in Table 3. In an embodiment of the invention, the LVL-modified TCR comprises (i) SEQ ID NO: 21, (ii) SEQ ID NO: 53, (iii) SEQ ID NO: 22, (iv) SEQ ID NO: 54, (v) SEQ ID NO: 34, (vi) SEQ ID NO: 35, (vii) SEQ ID NO: 61, (viii) SEQ ID NO: 62, (ix) both of SEQ ID NO: 21 and 22, (x) both of SEQ ID NOs: 53 and 22, (xi) both of SEQ ID NOs: 21 and 54, (xii) both of SEQ ID NOs: 53 and 54, (xiii) both of SEQ ID NOs: 34 and 35, or (xiv) both of SEQ ID NOs: 61 and 62, wherein all of SEQ ID NOs: 21-22, 34-35, 53, 54, 61 and 62 are as defined in Table 3.

TABLE 3

SEQ ID NO:	**Definitions of "X" in some embodiments**
SEQ ID NO: 17 (constant region α chain)	X at position 48 is Thr; X at position 112 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 112 is Leu, Ile, or Val; especially preferably wherein X at position 112 is Leu; X at position 114 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 114 is Leu, Ile, or Val; especially preferably wherein X at position 114 is Ile; and X at position 115 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 115 is Leu, Ile, or Val; especially preferably wherein X at position 115 is Val; Wherein SEQ ID NO: 17 does not comprise SEQ ID NO: 19 (unsubstituted constant region of α chain)
SEQ ID NO: 18 (constant region β chain)	X at position 57 is Ser
SEQ ID NO: 21 (4373 TCR α chain) (with wild type N-terminal signal peptide)	X at position 193 is Thr; X at position 257 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 257 is Leu, Ile, or Val; especially preferably wherein X at position 257 is Leu; X at position 259 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 259 is Leu, Ile, or Val; especially preferably wherein X at position 259 is Ile; and X at position 260 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 260 is Leu, Ile, or Val; especially preferably wherein X at position 260 is Val,

SEQ ID NO:	Definitions of "X" in some embodiments
	Wherein SEQ ID NO: 21 does not comprise SEQ ID NO: 23 (unsubstituted 4373 TCR α chain)
SEQ ID NO: 22 (4373 TCR β chain) (with variant N-terminal signal peptide)	X at position 191 is Ser
SEQ ID NO: 34 (4373 TCR α chain) (predicted sequence using IMGT without N-terminal signal peptide)	X at position 165 is Thr; X at position 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Leu; X at position 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 231 is Leu, Ile, or Val; especially preferably wherein X at position 231 is Ile; and X at position 232 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 232 is Leu, Ile, or Val; especially preferably wherein X at position 232 is Val, Wherein SEQ ID NO: 34 does not comprise SEQ ID NO: 36 (unsubstituted 4373 TCR α chain)
SEQ ID NO: 35 (4373 TCR β chain) (predicted sequence using IMGT without N-terminal signal peptide)	X at position 172 is Ser
SEQ ID NO: 53 (4373 TCR α chain) (with variant N-terminal signal peptide)	X at position 193 is Thr; X at position 257 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 257 is Leu, Ile, or Val; especially preferably wherein X at position 257 is Leu; X at position 259 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 259 is Leu, Ile, or Val; especially preferably wherein X at position 259 is Ile; and X at position 260 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 260 is Leu, Ile, or Val; especially preferably wherein X at position 260 is Val,

SEQ ID NO:	**Definitions of "X" in some embodiments**
	Wherein SEQ ID NO: 53 does not comprise SEQ ID NO: 55 (unsubstituted 4373 TCR α chain)
SEQ ID NO: 54 (4373 TCR β chain) (with wild type N-terminal signal peptide)	X at position 191 is Ser
SEQ ID NO: 61 (4373 TCR α chain) (predicted sequence using SignalP without N-terminal signal peptide)	X at position 172 is Thr; X at position 236 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Leu; X at position 238 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 231 is Leu, Ile, or Val; especially preferably wherein X at position 231 is Ile; and X at position 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 232 is Leu, Ile, or Val; especially preferably wherein X at position 232 is Val, Wherein SEQ ID NO: 61 does not comprise SEQ ID NO: 63 (unsubstituted 4373 TCR α chain)
SEQ ID NO: 62 (4373 TCR β chain) (predicted sequence using SignalP without N-terminal signal peptide)	X at position 170 is Ser

[0050] In an embodiment of the invention, the substituted amino acid sequence includes the cysteine substitutions in the constant region of one or both of the α and β chains in combination with the substitution(s) of one, two, or three amino acids in the transmembrane (TM) domain of the constant region of the α chain with a hydrophobic amino acid (also referred to herein as "cysteine-substituted, LVL-modified TCR"). In this regard, the TCR is a cysteine-substituted, LVL-modified, chimeric TCR in which the native Thr48 of SEQ ID NO: 19 is substituted with Cys; one, two, or three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 19 are, independently, substituted with Ala, Val, Leu, Ile, Pro, Phe, Met, or

Trp; preferably with Leu, Ile, or Val; and the native Ser57 of SEQ ID NO: 20 is substituted with Cys. Preferably, all three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 19 may, independently, be substituted with Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably with Leu, Ile, or Val. In an embodiment of the invention, the cysteine-substituted, LVL-modified TCR comprises (i) SEQ ID NO: 17, (ii) SEQ ID NO: 18, or (iii) both of SEQ ID NOs: 17 and 18, wherein both of SEQ ID NOs: 17 and 18 are as defined in Table 4. The cysteine-substituted, LVL-modified TCRs of the invention may include the substituted constant region in addition to any of the CDRs or variable regions described herein.

[0051] In an embodiment, the cysteine-substituted, LVL-modified TCR comprises a full-length α chain and a full-length β chain. In an embodiment of the invention, the cysteine-substituted, LVL-modified TCR comprises (i) SEQ ID NO: 21, (ii) SEQ ID NO: 53, (iii) SEQ ID NO: 22, (iv) SEQ ID NO: 54, (v) SEQ ID NO: 34, (vi) SEQ ID NO: 35, (vii) SEQ ID NO: 61, (viii) SEQ ID NO: 62, (ix) both of SEQ ID NO: 21 and 22, (x) both of SEQ ID NOs: 53 and 22, (xi) both of SEQ ID NOs: 21 and 54, (xii) both of SEQ ID NOs: 53 and 54, (xiii) both of SEQ ID NOs: 34 and 35, or (xiv) both of SEQ ID NOs: 61 and 62, wherein all of SEQ ID NOs: 21-22, 34-35, 53, 54, 61 and 62 are as defined in Table 4.

TABLE 4

SEQ ID NO:	**Definitions of "X" in some embodiments**
SEQ ID NO: 17 (constant region α chain)	X at position 48 is Cys; X at position 112 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 112 is Leu, Ile, or Val; especially preferably wherein X at position 112 is Leu; X at position 114 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 114 is Leu, Ile, or Val; especially preferably wherein X at position 114 is Ile; and X at position 115 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 115 is Leu, Ile, or Val; and especially preferably wherein X at position 115 is Val, wherein SEQ ID NO: 17 does not simultaneously comprise all of Ser at position 112, Met at position 114, and Gly at position 115.

SEQ ID NO:	**Definitions of "X" in some embodiments**
SEQ ID NO: 18 (constant region β chain)	X at position 57 is Cys
SEQ ID NO: 21 (4373 TCR α chain) (with wild type N-terminal signal peptide)	X at position 193 is Cys; X at position 257 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 257 is Leu, Ile, or Val; especially preferably wherein X at position 257 is Leu; X at position 259 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 259 is Leu, Ile, or Val; especially preferably wherein X at position 259 is Ile; and X at position 260 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 260 is Leu, Ile, or Val; and especially preferably wherein X at position 260 is Val, wherein SEQ ID NO: 21 does not simultaneously comprise all of Ser at position 257, Met at position 259, and Gly at position 260.
SEQ ID NO: 22 (4373 TCR β chain) (with variant N-terminal signal peptide)	X at position 191 is Cys
SEQ ID NO: 34 (4373 TCR α chain) (predicted sequence using IMGT without N-terminal signal peptide)	X at position 165 is Cys; X at position 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Leu; X at position 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 231 is Leu, Ile, or Val; especially preferably wherein X at position 231 is Ile; and X at position 232 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 232 is Leu, Ile, or Val; and especially preferably wherein X at position 232 is Val, wherein SEQ ID NO: 34 does not simultaneously comprise all of Ser at position 229, Met at position 231, and Gly at position 232.
SEQ ID NO: 35 (4373 TCR β chain) (predicted sequence using IMGT	X at position 172 is Cys

SEQ ID NO:	**Definitions of "X" in some embodiments**
without N-terminal signal peptide)	
SEQ ID NO: 53 (4373 TCR α chain) (with variant N-terminal signal peptide)	X at position 193 is Cys; X at position 257 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 257 is Leu, Ile, or Val; especially preferably wherein X at position 257 is Leu; X at position 259 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 259 is Leu, Ile, or Val; especially preferably wherein X at position 259 is Ile; and X at position 260 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 260 is Leu, Ile, or Val; and especially preferably wherein X at position 260 is Val, wherein SEQ ID NO: 53 does not simultaneously comprise all of Ser at position 257, Met at position 259, and Gly at position 260.
SEQ ID NO: 54 (4373 TCR β chain) (with wild type N-terminal signal peptide)	X at position 191 is Cys
SEQ ID NO: 61 (4373 TCR α chain) (predicted sequence using SignalP without N-terminal signal peptide)	X at position 172 is Cys; X at position 236 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Leu; X at position 238 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 231 is Leu, Ile, or Val; especially preferably wherein X at position 231 is Ile; and X at position 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 232 is Leu, Ile, or Val; and especially preferably wherein X at position 232 is Val, wherein SEQ ID NO: 61 does not simultaneously comprise all of Ser at position 229, Met at position 231, and Gly at position 232.
SEQ ID NO: 62 (4373 TCR β chain) (predicted sequence using SignalP without	X at position 170 is Cys

SEQ ID NO:	Definitions of "X" in some embodiments
N-terminal signal peptide)	

[0052] In an embodiment of the invention, the cysteine-substituted, LVL-modified TCR comprises (a) SEQ ID NO: 38 (α chain constant region of cysteine-substituted, LVL-modified TCR); (b) SEQ ID NO: 39 (β chain constant region of cysteine-substituted, LVL-modified TCR); (c) SEQ ID NO: 40 (α chain of cysteine-substituted, LVL-modified 4373 TCR with wild type N-terminal signal sequence); (d) SEQ ID NO: 41 (β chain of cysteine-substituted, LVL-modified 4373 TCR with variant N-terminal signal sequence); (e) SEQ ID NO: 42 (α chain of cysteine-substituted, LVL-modified 4373 TCR without N-terminal signal sequence predicted by IMGT); (f) SEQ ID NO: 43 (β chain of cysteine-substituted, LVL-modified 4373 TCR without N-terminal signal sequence predicted by IMGT); (g) SEQ ID NO: 65 (α chain of cysteine-substituted, LVL-modified 4373 TCR without N-terminal signal sequence predicted by SignalP); (h) SEQ ID NO: 66 (β chain of cysteine-substituted, LVL-modified 4373 TCR without N-terminal signal sequence predicted by SignalP); (i) SEQ ID NO: 57 (α chain of cysteine-substituted, LVL-modified 4373 TCR with variant N-terminal signal sequence); (j) SEQ ID NO: 58 (β chain of cysteine-substituted, LVL-modified 4373 TCR with wild type N-terminal signal sequence); (k) both (a) and (b); (l) both (c) and (d); (m) both (e) and (f); (n) both (g) and (h); or (o) both (i) and (j).

[0053] Also provided by the invention is a polypeptide comprising a functional portion of any of the TCRs described herein. The term "polypeptide," as used herein, includes oligopeptides and refers to a single chain of amino acids connected by one or more peptide bonds.

[0054] With respect to the inventive polypeptides, the functional portion can be any portion comprising contiguous amino acids of the TCR of which it is a part, provided that the functional portion specifically binds to G12D RAS. The term "functional portion," when used in reference to a TCR, refers to any part or fragment of the TCR of the invention, which part or fragment retains the biological activity of the TCR of which it is a part (the parent TCR). Functional portions encompass, for example, those parts of a TCR that retain the ability to specifically bind to G12D RAS (e.g., within the context of an HLA-A*11:01

molecule), or detect, treat, or prevent cancer, to a similar extent, the same extent, or to a higher extent, as the parent TCR. In reference to the parent TCR, the functional portion can comprise, for instance, about 10%, about 25%, about 30%, about 50%, about 68%, about 80%, about 90%, about 95%, or more, of the parent TCR.

[0055] The functional portion can comprise additional amino acids at the amino or carboxy terminus of the portion, or at both termini, which additional amino acids are not found in the amino acid sequence of the parent TCR. Desirably, the additional amino acids do not interfere with the biological function of the functional portion, e.g., specifically binding to G12D RAS; and/or having the ability to detect cancer, treat or prevent cancer, etc. More desirably, the additional amino acids enhance the biological activity, as compared to the biological activity of the parent TCR.

[0056] The polypeptide can comprise a functional portion of either or both of the α and β chains of the TCRs of the invention, such as a functional portion comprising one or more of the CDR1, CDR2, and CDR3 of the variable region(s) of the α chain and/or β chain of a TCR of the invention. In an embodiment of the invention, the polypeptide can comprise the amino acid sequence of SEQ ID NO: 1 (CDR1 of α chain), SEQ ID NO: 2 (CDR2 of α chain), SEQ ID NO: 3 (CDR3 of α chain), SEQ ID NO: 4 (CDR1 of β chain), SEQ ID NO: 5 (CDR2 of β chain), SEQ ID NO: 6 (CDR3 of β chain), or a combination thereof.

[0057] In this regard, the inventive polypeptide can comprise any one or more of the amino acid sequences selected from any of SEQ ID NOs: 1-6. In an embodiment of the invention, the TCR comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, or (c) all of SEQ ID NOs: 1-6. In a preferred embodiment, the polypeptide comprises the amino acid sequences of all of SEQ ID NOs: 1-6. The CDR3 of SEQ ID NO: 3 or 6, i.e., of the α chain or β chain or both, may further comprise a cysteine immediately N-terminal to the first amino acid of the CDR or a phenylalanine immediately C-terminal to the final amino acid or both.

[0058] In an embodiment of the invention, the inventive polypeptide can comprise, for instance, the variable region of the inventive TCR comprising a combination of the CDR regions set forth above. In this regard, the polypeptide can comprise the amino acid sequence of (i) SEQ ID NO: 7 (variable region of α chain with wild type N-terminal signal sequence), (ii) SEQ ID NO: 51 (variable region of α chain of 4373 TCR with variant N-terminal signal sequence); (iii) SEQ ID NO: 8 (variable region of β chain with variant N-terminal signal sequence), (iv) SEQ ID NO: 52 (variable region of β chain with wild type N-terminal signal sequence), (v) both of SEQ ID NOs: 7 and 8; (vi) both of SEQ ID NOs: 51 and 8, (vii) both of SEQ ID NOs: 7 and 52, or (viii) both of SEQ ID NOs: 51 and 52, (ix) SEQ ID NO: 32 (variable region of α chain without N-terminal signal sequence predicted with IMGT), (x) SEQ ID NO: 33 (variable region of β chain without N-terminal signal sequence predicted with IMGT), (xi) SEQ ID NO: 59 (variable region of α chain of 4373 TCR without N-terminal signal peptide predicted with SignalP); (xii) SEQ ID NO: 60 (variable region of β chain of 4373 TCR without N-terminal signal peptide predicted with SignalP); (xiii) both of SEQ ID NOs: 32 and 33 or both of SEQ ID NOs: 59 and 60. Preferably, the polypeptide comprises the amino acid sequences of (i) both of SEQ ID NOs: 7 and 8, (ii) both of SEQ ID NOs: 51 and 52, (iii) both of SEQ ID NOs: 32 and 33 or (iv) both of SEQ ID NOs: 59 and 60.

[0059] In an embodiment of the invention, the inventive polypeptide can further comprise the constant region of the inventive TCR set forth above. In this regard, the polypeptide can further comprise the amino acid sequence of SEQ ID NO: 19 (WT murine constant region of α chain), SEQ ID NO: 20 (WT murine constant region of β chain), SEQ ID NO: 17 (substituted murine constant region of α chain), SEQ ID NO: 18 (substituted murine constant region of β chain), SEQ ID NO: 38 (α chain constant region of cysteine-substituted, LVL-modified TCR); SEQ ID NO: 39 (β chain constant region of cysteine-substituted, LVL-modified TCR); both SEQ ID NOs: 19 and 20, both SEQ ID NOs: 17 and 18, or both SEQ ID NOs: 38 and 39. Preferably, the polypeptide further comprises the amino acid sequences of both of SEQ ID NOs: 17 and 18, both of SEQ ID NO: 19 and 20, or both of SEQ ID NOs: 38 and 39 in combination with any of the CDR regions or variable regions described herein with respect to other aspects of the invention. In an embodiment of the invention, one or both of SEQ ID NOs: 17 and 18 of the polypeptide are as defined in any one of Tables 2-4. The α chain constant regions provided herein are shown with an N-terminal asparagine. In some embodiments, the N-terminal amino acid of the α chain constant regions described herein is aspartic acid.

[0060] In an embodiment of the invention, the inventive polypeptide can comprise the entire length of an α or β chain of the TCR described herein. In this regard, the inventive polypeptide can comprise the amino acid sequence of SEQ ID NO: 21, SEQ ID NO: 53, SEQ

ID NO: 22, SEQ ID NO: 54, SEQ ID NO: 23, SEQ ID NO: 55, SEQ ID NO: 24, SEQ ID NO: 56, SEQ ID NO: 34, SEQ ID NO: 61, SEQ ID NO: 35, SEQ ID NO: 62, SEQ ID NO: 36, SEQ ID NO: 63, SEQ ID NO: 37, SEQ ID NO: 64, SEQ ID NO: 40, SEQ ID NO: 57, SEQ ID NO: 41, SEQ ID NO: 58, SEQ ID NO: 42, SEQ ID NO: 65, SEQ ID NO: 43, SEQ ID NO: 66, both of SEQ ID NOs: 21-22, both of SEQ ID NOs: 21 and 54, both of SEQ ID NOs: 53 and 22, both of SEQ ID NOs: 53 and 54, both of SEQ ID NOs: 23-24, both of SEQ ID NOs: 55 and 24, both of SEQ ID NOs: 23 and 54, both of SEQ ID NOs: 55 and 54, both of SEQ ID NOs: 34-35, both of SEQ ID NOs: 36-37, both of SEQ ID NOs: 40-41, both of SEQ ID NOs: 57 and 41, both of SEQ ID NOs: 40-58, both of SEQ ID NOs: 57-58, both of SEQ ID NOs: 42-43, both of SEQ ID NOs: 61 and 62, both of SEQ ID NOs: 63 and 64 or both of SEQ ID NOs: 65 and 66. Alternatively, the polypeptide of the invention can comprise both chains of the TCRs described herein.

[0061] For example, the polypeptide of the invention can comprise (a) the amino acid sequence of SEQ ID NO: 21, wherein: (i) X at position 193 of SEQ ID NO: 21 is Thr or Cys; (ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (b) the amino acid sequence of SEQ ID NO: 53, wherein: (i) X at position 193 of SEQ ID NO: 53 is Thr or Cys; (ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (c) the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys; (d) the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys; (e) both (a) and (c), (a) and (d), (b) and (c) or (b) and (d); (f) the amino acid sequence of SEQ ID NO: 34, wherein: (i) X at position 165 of SEQ ID NO: 34 is Thr or Cys; (ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (g) the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys; (h) the amino acid sequence of SEQ ID NO: 61, wherein: (i) X at position 172 of SEQ ID NO: 61 is Thr or Cys; (ii) X at position 236 of SEQ ID NO: 61 is

Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (i) the amino acid sequence of SEQ ID NO:62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys; (j) both (f) and (g) or both (h) and (i); (k) SEQ ID NO: 40; (l) SEQ ID NO: 57; (m) SEQ ID NO: 41; (n) SEQ ID NO: 58; (o) SEQ ID NO: 42; (p) SEQ ID NO: 43; (q) SEQ ID NO: 65; (r) SEQ ID NO: 66; (s) both (k) and (m); (t) both (l) and (m); (u) both (k) and (n); (v) both (l) and (n); (w) both (o) and (p); or (x) both (q) and (r). In an embodiment of the invention, any one or more of SEQ ID NOs: 21-22, 34-35, 53, 54, 61 and 62 of the polypeptide are as defined in any one of Tables 2-4.

[0062] The invention further provides a protein comprising at least one of the polypeptides described herein. By "protein" is meant a molecule comprising one or more polypeptide chains.

[0063] In an embodiment, the protein of the invention can comprise a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 1-3 and a second polypeptide chain comprising the amino acid sequence of SEQ ID NOs: 4-6. The CDR3 of SEQ ID NO: 3 or 6, i.e., of the α chain or β chain or both, may further comprise a cysteine immediately N-terminal to the first amino acid of the CDR or a phenylalanine immediately C-terminal to the final amino acid or both.

[0064] In another embodiment of the invention, (i) the first polypeptide chain of the protein may comprise the amino acid sequence of SEQ ID NO: 7 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 8; (ii) the first polypeptide chain of the protein may comprise the amino acid sequence of SEQ ID NO: 51 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 8; (iii) the first polypeptide chain of the protein may comprise the amino acid sequence of SEQ ID NO: 7 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 52; (iv) the first polypeptide chain of the protein may comprise the amino acid sequence of SEQ ID NO: 51 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 52; (v) the first polypeptide chain of the protein may comprise the amino acid sequence of SEQ ID NO: 32 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 33 or (vi) the first polypeptide chain of the protein may comprise the amino acid sequence of SEQ ID NO: 59 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 60.

[0065] The inventive protein may further comprise any of the constant regions described herein with respect to other aspects of the invention. In this regard, in an embodiment of the invention, (i) the first polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 17 and the second polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 18; (ii) the first polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 19 and the second polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 20; or (ii) the first polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 38 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 39. In an embodiment of the invention, one or both of SEQ ID NOs: 17 and 18 of the protein are as defined in any one of Tables 2-4.

[0066] Alternatively or additionally, the protein of an embodiment of the invention can comprise (a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21, wherein: (i) X at position 193 of SEQ ID NO: 21 is Thr or Cys; (ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (b) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 53, wherein: (i) X at position 193 of SEQ ID NO: 53 is Thr or Cys; (ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (c) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys; (d) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys; (e) both (a) and (c), (a) and (d), (b) and (c) or (b) and (d); (f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 34, wherein: (i) X at position 165 of SEQ ID NO: 34 is Thr or Cys; (ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (g) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys; (h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61, wherein: (i) X at position 172 of SEQ ID NO: 61 is Thr or Cys; (ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (i) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62 (β chain of 4373 TCR without N-terminal signal peptide predicted with SignalP), wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys or (j) both (f) or both (h) and (i) and; (k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 40; (k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 57; (m) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 41; (n) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 58; (o) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 42; (p) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 43; (p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 65; (q) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 66; (s) both (k) and (m); (t) both (l) and (m); (u) both (k) and (n); (v) both (m) and (n); (w) both (o) and (p) or both (q) and (r). In an embodiment of the invention, one or more of SEQ ID NOs: 21-22, 34-35, 53, 54, 61 and 62 are as defined in any one of Tables 2-4.

[0067] The protein of the invention can be a TCR. Alternatively, if, for example, the protein comprises a single polypeptide chain comprising the amino acid sequences of both SEQ ID NOs: 23 and 24, both SEQ ID NOs: 55 and 24, both SEQ ID NOs: 23 and 56, both SEQ ID NOs: 55 and 56, both SEQ ID NOs: 21 and 22, both SEQ ID NOs: 53 and 22, both SEQ ID NOs: 21 and 54, both SEQ ID NOs: 53 and 54, or if the first and/or second polypeptide chain(s) of the protein further comprise(s) other amino acid sequences, e.g., an amino acid sequence encoding an immunoglobulin or a portion thereof, then the inventive protein can be a fusion protein. In this regard, the invention also provides a fusion protein comprising at least one of the inventive polypeptides described herein along with at least one other polypeptide. The other polypeptide can exist as a separate polypeptide of the fusion protein, or can exist as a polypeptide, which is expressed in frame (in tandem) with one of the inventive polypeptides described herein. The other polypeptide can encode any peptidic or proteinaceous molecule, or a portion thereof, including, but not limited to an immunoglobulin, CD3, CD4, CD8, an MHC molecule, a CD1 molecule, e.g., CD1a, CD1b, CD1c, CD1d, etc.

[0068] The fusion protein can comprise one or more copies of the inventive polypeptide and/or one or more copies of the other polypeptide. For instance, the fusion protein can comprise 1, 2, 3, 4, 5, or more, copies of the inventive polypeptide and/or of the other polypeptide. Suitable methods of making fusion proteins are known in the art, and include, for example, recombinant methods.

[0069] In some embodiments of the invention, the TCRs, polypeptides, and proteins of the invention may be expressed as a single protein comprising a linker peptide linking the α chain and the β chain. In this regard, the TCRs, polypeptides, and proteins of the invention may further comprise a linker peptide. The linker peptide may advantageously facilitate the expression of a recombinant TCR, polypeptide, and/or protein in a host cell. The linker peptide may comprise any suitable amino acid sequence. The linker peptide may be a cleavable linker peptide. For example, the linker peptide may be a furin-SGSG-P2A linker comprising the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 25). Upon expression of the construct including the linker peptide by a host cell, the linker peptide may be cleaved, resulting in separated α and β chains. In an embodiment of the invention, the TCR, polypeptide, or protein may comprise an amino acid sequence comprising a full-length α chain, a full-length β chain, and a linker peptide positioned between the α and β chains, for example α chain–linker–β chain or β chain–linker–α chain.

[0070] In an embodiment of the invention, the TCR, polypeptide, or protein may comprise an amino acid sequence as set forth in SEQ ID NO: 47 comprising from N-terminus to C-terminus, a β chain, a linker (SEQ ID NO:25) and an α chain. The variant comprises a β chain variable region (with a variant signal peptide) as set forth in SEQ ID NO: 8 and a modified β constant domain as set forth in SEQ ID NO:39. The full-length β chain of the variant is set forth in SEQ ID NO: 41. The variant also comprises an α chain variable region (with a wild type signal peptide) as set forth in SEQ ID NO: 7 and a modified α constant domain as set forth in SEQ ID NO:38. The full-length α chain of the variant is set forth in SEQ ID NO: 40.

[0071] In another embodiment of the invention, the TCR, polypeptide, or protein may comprise an amino acid sequence as set forth in SEQ ID NO: 67 comprising from N-terminus to C-terminus, an α chain, a linker (SEQ ID NO:25) and a β chain. The variant comprises an α chain variable region (with a variant signal peptide) as set forth in SEQ ID NO: 51 and a modified α constant domain as set forth in SEQ ID NO:38. The full-length α chain of the variant is set forth in SEQ ID NO: 57. The variant also comprises a β chain variable region (with a wild type signal peptide) as set forth in SEQ ID NO: 52 and a modified β constant domain as set forth in SEQ ID NO:39. The full-length β chain of the variant is set forth in SEQ ID NO: 58.

[0072] In some embodiments, the TCR, polypeptide or protein disclosed herein comprises an α chain and/or a β chain, as disclosed herein, comprising a signal peptide. In some embodiments, the sequence of the signal peptide of any of the α chains and/or β chains disclosed herein comprises an alanine or histidine residue substituted for the wild-type residue at position 2.

[0073] In some embodiments, the TCR, polypeptide or protein disclosed herein comprises a mature version of an α chain and/or a β chain, as disclosed herein, that lacks a signal peptide. The sequence of the signal peptide or mature form of the α chain and/or a β chain can be performed according to any method known in the art including IMGT and SignalP.

[0074] The protein of the invention can be a recombinant antibody, or an antigen binding portion thereof, comprising at least one of the inventive polypeptides described herein. As used herein, "recombinant antibody" refers to a recombinant (e.g., genetically engineered) protein comprising at least one of the polypeptides of the invention and a polypeptide chain of an antibody, or an antigen binding portion thereof. The polypeptide of an antibody, or antigen binding portion thereof, can be a heavy chain, a light chain, a variable or constant region of a heavy or light chain, a single chain variable fragment (scFv), or an Fc, Fab, or $F(ab)_2'$ fragment of an antibody, etc. The polypeptide chain of an antibody, or an antigen binding portion thereof, can exist as a separate polypeptide of the recombinant antibody. Alternatively, the polypeptide chain of an antibody, or an antigen binding portion thereof, can exist as a polypeptide, which is expressed in frame (in tandem) with the polypeptide of the invention. The polypeptide of an antibody, or an antigen binding portion thereof, can be a polypeptide of any antibody or any antibody fragment, including any of the antibodies and antibody fragments described herein.

[0075] Included in the scope of the invention are functional variants of the inventive TCRs, polypeptides, or proteins described herein. The term "functional variant," as used herein, refers to a TCR, polypeptide, or protein having substantial or significant sequence identity or similarity to a parent TCR, polypeptide, or protein, which functional variant retains the biological activity of the TCR, polypeptide, or protein of which it is a variant. Functional variants encompass, for example, those variants of the TCR, polypeptide, or protein described herein (the parent TCR, polypeptide, or protein) that retain the ability to specifically bind to the G12D RAS for which the parent TCR has antigenic specificity or to which the parent polypeptide or protein specifically binds, to a similar extent, the same extent, or to a higher extent, as the parent TCR, polypeptide, or protein. In reference to the parent TCR, polypeptide, or protein, the functional variant can, for instance, be at least about 30%, about 50%, about 75%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or more identical in amino acid sequence to the parent TCR, polypeptide, or protein, respectively.

[0076] The functional variant can, for example, comprise the amino acid sequence of the parent TCR, polypeptide, or protein with at least one conservative amino acid substitution. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same chemical or physical properties. For instance, the conservative amino acid substitution can be an acidic amino acid substituted for another acidic amino acid (e.g., Asp or Glu), an amino acid with a nonpolar side chain substituted for another amino acid with a nonpolar side chain (e.g., Ala, Gly, Val, Ile, Leu, Met, Phe, Pro, Trp, Val, etc.), a basic amino acid substituted for another basic amino acid (Lys, Arg, etc.), an amino acid with a polar side chain substituted for another amino acid with a polar side chain (Asn, Cys, Gln, Ser, Thr, Tyr, etc.), etc.

[0077] Alternatively or additionally, the functional variants can comprise the amino acid sequence of the parent TCR, polypeptide, or protein with at least one non-conservative amino acid substitution. In this case, it is preferable for the non-conservative amino acid substitution to not interfere with or inhibit the biological activity of the functional variant.

Preferably, the non-conservative amino acid substitution enhances the biological activity of the functional variant, such that the biological activity of the functional variant is increased as compared to the parent TCR, polypeptide, or protein.

[0078] Each signal peptide of the TCRs, polypeptides, proteins, functional variants, and functional portions described herein, when present, can be any suitable TCR signal peptide, so long as the TCR, polypeptide, protein, or functional variant is expressed and has antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid presented by an HLA Class I molecule.

[0079] The TCR, polypeptide, or protein can consist essentially of the specified amino acid sequence or sequences described herein, such that other components of the TCR, polypeptide, or protein, e.g., other amino acids, do not materially change the biological activity of the TCR, polypeptide, or protein. In this regard, the inventive TCR, polypeptide, or protein can, for example, consist essentially of the amino acid sequence of SEQ ID NO: 21, SEQ ID NO: 53, SEQ ID NO: 22, SEQ ID NO: 54, SEQ ID NO: 23, SEQ ID NO: 55, SEQ ID NO: 24, SEQ ID NO: 56, SEQ ID NO: 34, SEQ ID NO: 61, SEQ ID NO: 35, SEQ ID NO: 62, SEQ ID NO: 36, SEQ ID NO: 63, SEQ ID NO: 37, SEQ ID NO: 64, SEQ ID NO: 40, SEQ ID NO: 57, SEQ ID NO: 41, SEQ ID NO: 58, SEQ ID NO: 42, SEQ ID NO: 65, SEQ ID NO: 43, SEQ ID NO: 66, both of SEQ ID NOs: 21-22, both of SEQ ID NOs: 53 and 22, both of SEQ ID NOs: 21 and 54, both of SEQ ID NOs: 53 and 54, both of SEQ ID NOs: 23-24, both of SEQ ID NOs: 55 and 24, both of SEQ ID NOs: 23 and 54, both of SEQ ID NOs: 55 and 56, both of SEQ ID NOs: 34-35, both of SEQ ID NOs: 61-62, both of SEQ ID NOs: 36-37, both of SEQ ID NOs: 63-64, both of SEQ ID NOs: 40-41, both of SEQ ID NOs: 57 and 41, both of SEQ ID NOs: 40 and 58, both of SEQ ID NOs: 57 and 58, both of SEQ ID NOs: 42-43 or both of SEQ ID NOs: 65-66. Also, for instance, the inventive TCRs, polypeptides, or proteins can consist essentially of the amino acid sequence(s) of (i) SEQ ID NO: 7, (ii) SEQ ID NO: 51, (iii) SEQ ID NO: 8, (iv) SEQ ID NO: 52, (v) SEQ ID NO: 32, (vi) SEQ ID NO: 33 (vii) SEQ ID NO: 59 or (viii) SEQ ID NO: 60. Furthermore, the inventive TCRs, polypeptides, or proteins can consist essentially of the amino acid sequences of (a) any one or more of SEQ ID NOs: 1-6; (b) all of SEQ ID NO: 1-3; (c) all of SEQ ID NO: 4-6; or (d) all of SEQ ID NOs: 1-6.

[0080] The TCRs, polypeptides, and proteins of the invention can be of any length, i.e., can comprise any number of amino acids, provided that the TCRs, polypeptides, or proteins retain their biological activity, e.g., the ability to specifically bind to G12D RAS; detect cancer in a mammal; or treat or prevent cancer in a mammal, etc. For example, the polypeptide can be in the range of from about 50 to about 5000 amino acids long, such as about 50, about 70, about 75, about 100, about 125, about 150, about 175, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1000 or more amino acids in length. In this regard, the polypeptides of the invention also include oligopeptides.

[0081] The TCRs, polypeptides, and proteins of the invention can comprise synthetic amino acids in place of one or more naturally-occurring amino acids. Such synthetic amino acids are known in the art, and include, for example, aminocyclohexane carboxylic acid, norleucine, α-amino n-decanoic acid, homoserine, S-acetylaminomethyl-cysteine, trans-3- and trans-4-hydroxyproline, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine β-hydroxyphenylalanine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aminomalonic acid, aminomalonic acid monoamide, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α-aminocyclopentane carboxylic acid, α-aminocyclohexane carboxylic acid, α-aminocycloheptane carboxylic acid, α-(2-amino-2-norbornane)-carboxylic acid, α,γ-diaminobutyric acid, α,β-diaminopropionic acid, homophenylalanine, and α-tert-butylglycine.

[0082] The TCRs, polypeptides, and proteins of the invention can be, e.g., glycosylated, amidated, carboxylated, phosphorylated, esterified, N-acylated, cyclized via, e.g., a disulfide bridge, or converted into an acid addition salt and/or optionally dimerized or polymerized, or conjugated.

[0083] The TCR, polypeptide, and/or protein of the invention can be obtained by methods known in the art such as, for example, *de novo* synthesis. Also, polypeptides and proteins can be recombinantly produced using the nucleic acids described herein using standard recombinant methods. See, for instance, Green and Sambrook, Molecular Cloning: A

Laboratory Manual, 4th ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (2012). Alternatively, the TCRs, polypeptides, and/or proteins described herein can be commercially synthesized by any of a variety of commercial entities. In this respect, the inventive TCRs, polypeptides, and proteins can be synthetic, recombinant, isolated, and/or purified. An embodiment of the invention provides an isolated or purified TCR, polypeptide, or protein encoded by any of the nucleic acids or vectors described herein with respect to other aspects of the invention. Another embodiment of the invention provides an isolated or purified TCR, polypeptide, or protein that results from expression of any of the nucleic acids or vectors described herein with respect to other aspects of the invention in a cell. Still another embodiment of the invention provides a method of producing any of the TCRs, polypeptides, or proteins described herein, the method comprising culturing any of the host cells or populations of host cells described herein so that the TCR, polypeptide, or protein is produced.

[0084] Included in the scope of the invention are conjugates, e.g., bioconjugates, comprising any of the inventive TCRs, polypeptides, or proteins (including any of the functional portions or variants thereof), nucleic acids, recombinant expression vectors, host cells, populations of host cells, or antibodies, or antigen binding portions thereof. Conjugates, as well as methods of synthesizing conjugates in general, are known in the art.

[0085] An embodiment of the invention provides a nucleic acid comprising a nucleotide sequence encoding any of the TCRs, polypeptides, or proteins described herein. "Nucleic acid," as used herein, includes "polynucleotide," "oligonucleotide," and "nucleic acid molecule," and generally means a polymer of DNA or RNA, which can be single-stranded or double-stranded, which can contain natural, non-natural or altered nucleotides, and which can contain a natural, non-natural or altered internucleotide linkage, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified oligonucleotide. In an embodiment, the nucleic acid comprises complementary DNA (cDNA). It is generally preferred that the nucleic acid does not comprise any insertions, deletions, inversions, and/or substitutions. However, it may be suitable in some instances, as discussed herein, for the nucleic acid to comprise one or more insertions, deletions, inversions, and/or substitutions.

[0086] Preferably, the nucleic acids of the invention are recombinant. As used herein, the term "recombinant" refers to (i) molecules that are constructed outside living cells by joining natural or synthetic nucleic acid segments to nucleic acid molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above. For purposes herein, the replication can be *in vitro* replication or *in vivo* replication.

[0087] In an embodiment of the invention, the nucleic acid comprises the nucleotide sequence of (i) SEQ ID NO: 44 (nucleotide sequence encoding the variable region of the α chain of 4373 TCR), (ii) SEQ ID NO: 45 nucleotide sequence encoding the variable region of the β chain of 4373 TCR, or (iii) both of SEQ ID NOs: 44-45.

[0088] The nucleic acids can be constructed based on chemical synthesis and/or enzymatic ligation reactions using procedures known in the art. See, for example, Green and Sambrook et al., *supra.* For example, a nucleic acid can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed upon hybridization (e.g., phosphorothioate derivatives and acridine substituted nucleotides). Examples of modified nucleotides that can be used to generate the nucleic acids include, but are not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, β-D-galactosylqueosine, inosine, N^6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N^6-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, β-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N^6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine. Alternatively, one or more of the nucleic acids of the invention can be purchased from any of a variety of commercial entities.

[0089] The nucleic acid can comprise any nucleotide sequence which encodes any of the TCRs, polypeptides, or proteins described herein. In an embodiment of the invention, the nucleic acid comprises a codon-optimized nucleotide sequence encoding any of the TCRs, polypeptides, or proteins described herein. Without being bound to any particular theory or mechanism, it is believed that codon optimization of the nucleotide sequence increases the translation efficiency of the mRNA transcripts. Codon optimization of the nucleotide sequence may involve substituting a native codon for another codon that encodes the same amino acid, but can be translated by tRNA that is more readily available within a cell, thus increasing translation efficiency. Optimization of the nucleotide sequence may also reduce secondary mRNA structures that would interfere with translation, thus increasing translation efficiency.

[0090] The invention also provides a nucleic acid comprising a nucleotide sequence which is complementary to the nucleotide sequence of any of the nucleic acids described herein or a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of any of the nucleic acids described herein.

[0091] The nucleotide sequence which hybridizes under stringent conditions preferably hybridizes under high stringency conditions. By “high stringency conditions” is meant that the nucleotide sequence specifically hybridizes to a target sequence (the nucleotide sequence of any of the nucleic acids described herein) in an amount that is detectably stronger than non-specific hybridization. High stringency conditions include conditions which would distinguish a polynucleotide with an exact complementary sequence, or one containing only a few scattered mismatches from a random sequence that happened to have a few small regions (e.g., 3-10 bases) that matched the nucleotide sequence. Such small regions of complementarity are more easily melted than a full-length complement of 14-17 or more bases, and high stringency hybridization makes them easily distinguishable. Relatively high stringency conditions would include, for example, low salt and/or high temperature conditions, such as provided by about 0.02-0.1 M NaCl or the equivalent, at temperatures of about 50-70 °C. Such high stringency conditions tolerate little, if any, mismatch between the nucleotide sequence and the template or target strand, and are particularly suitable for detecting expression of any of the inventive TCRs. It is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide.

[0092] An embodiment of the invention also provides a nucleic acid comprising a nucleotide sequence that is at least about 70% or more, e.g., about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any of the nucleic acids described herein. In this regard, the nucleic acid may consist essentially of any of the nucleotide sequences described herein.

[0093] An embodiment of the invention provides an isolated or purified nucleic acid comprising, from 5’ to 3’, a first nucleic acid sequence and a second nucleotide sequence, wherein the first and second nucleotide sequence, respectively, encode the amino sequences of SEQ ID NOs: 7 and 8; 51 and 8; 7 and 52; 51 and 52; 8 and 7; 8 and 51; 52 and 7; 52 and 51; 21 and 22; 21 and 54; 53 and 22; 53 and 54; 22 and 21; 54 and 21; 22 and 53; 54 and 53; 23 and 24; 55 and 24; 23 and 56; 55 and 56; 24 and 23; 24 and 55; 56 and 55; 56 and 23; 32 and 33; 33 and 32; 59 and 60; 60 and 59; 34 and 35; 35 and 34; 61 and 62; 62 and 61; 36 and 37; 37 and 36; 63 and 64; 64 and 63; 40 and 41; 57 and 41; 40 and 58; 57 and 58; 41 and 40; 41 and 57; 58 and 40; 58 and 57; 42 and 43; 43 and 42; 65 and 66; or 66 and 65.

[0094] In an embodiment of the invention, the isolated or purified nucleic acid further comprises a third nucleotide sequence interposed between the first and second nucleotide sequence, wherein the third nucleotide sequence encodes a cleavable linker peptide. In an embodiment of the invention, the cleavable linker peptide comprises the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 25).

[0095] The nucleic acids of the invention can be incorporated into a recombinant expression vector. In this regard, the invention provides a recombinant expression vector comprising any of the nucleic acids of the invention. In an embodiment of the invention, the recombinant expression vector comprises a nucleotide sequence encoding the α chain, the β chain, and linker peptide.

[0096] For purposes herein, the term "recombinant expression vector" means a genetically-modified oligonucleotide or polynucleotide construct that permits the expression of an mRNA, protein, polypeptide, or peptide by a host cell, when the construct comprises a nucleotide sequence encoding the mRNA, protein, polypeptide, or peptide, and the vector is contacted with the cell under conditions sufficient to have the mRNA, protein, polypeptide, or peptide expressed within the cell. The vectors of the invention are not naturally-occurring as a whole. However, parts of the vectors can be naturally-occurring. The inventive recombinant expression vectors can comprise any type of nucleotide, including, but not limited to DNA and RNA, which can be single-stranded or double-stranded, synthesized or obtained in part from natural sources, and which can contain natural, non-natural or altered nucleotides. The recombinant expression vectors can comprise naturally-occurring, non-naturally-occurring internucleotide linkages, or both types of linkages. Preferably, the non-naturally occurring or altered nucleotides or internucleotide linkages do not hinder the transcription or replication of the vector.

[0097] The recombinant expression vector of the invention can be any suitable recombinant expression vector, and can be used to transform or transfect any suitable host cell. Suitable vectors include those designed for propagation and expansion or for expression or both, such as plasmids and viruses. The vector can be selected from the pUC series (Fermentas Life Sciences), the pBluescript series (Stratagene, LaJolla, CA), the pET series (Novagen, Madison, WI), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, CA). Bacteriophage vectors, such as λGT10, λGT11, λZapII (Stratagene), λEMBL4, and λNM1149, also can be used. Examples of plant expression vectors include pBI01, pBI101.2, pBI101.3, pBI121 and pBIN19 (Clontech). Examples of animal expression vectors include pEUK-Cl, pMAM and pMAMneo (Clontech). Preferably, the recombinant expression vector is a viral vector, e.g., a retroviral vector. In an especially preferred embodiment, the recombinant expression vector is an MSGV1 vector. In an embodiment of the invention, the recombinant expression vector is a transposon or a lentiviral vector.

[0098] The recombinant expression vectors of the invention can be prepared using standard recombinant DNA techniques described in, for example, Green and Sambrook et al., *supra*. Constructs of expression vectors, which are circular or linear, can be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived, e.g., from ColEl, 2 μ plasmid, λ, SV40, bovine papillomavirus, and the like.

[0099] Desirably, the recombinant expression vector comprises regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host cell (e.g., bacterium, fungus, plant, or animal) into which the vector is to be introduced, as appropriate and taking into consideration whether the vector is DNA- or RNA-based.

[0100] The recombinant expression vector can include one or more marker genes, which allow for selection of transformed or transfected host cells. Marker genes include biocide resistance, e.g., resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host cell to provide prototrophy, and the like. Suitable marker genes for the inventive expression vectors include, for instance, neomycin/G418 resistance genes, hygromycin resistance genes, histidinol resistance genes, tetracycline resistance genes, and ampicillin resistance genes.

[0101] The recombinant expression vector can comprise a native or nonnative promoter operably linked to the nucleotide sequence encoding the TCR, polypeptide, or protein, or to the nucleotide sequence which is complementary to or which hybridizes to the nucleotide sequence encoding the TCR, polypeptide, or protein. The selection of promoters, e.g., strong, weak, inducible, tissue-specific and developmental-specific, is within the ordinary skill of the artisan. Similarly, the combining of a nucleotide sequence with a promoter is also within the skill of the artisan. The promoter can be a non-viral promoter or a viral promoter, e.g., a cytomegalovirus (CMV) promoter, an SV40 promoter, an RSV promoter, and a promoter found in the long-terminal repeat of the murine stem cell virus.

[0102] The inventive recombinant expression vectors can be designed for either transient expression, for stable expression, or for both. Also, the recombinant expression vectors can be made for constitutive expression or for inducible expression.

[0103] Further, the recombinant expression vectors can be made to include a suicide gene. As used herein, the term "suicide gene" refers to a gene that causes the cell expressing the suicide gene to die. The suicide gene can be a gene that confers sensitivity to an agent, e.g., a drug, upon the cell in which the gene is expressed, and causes the cell to die when the cell is contacted with or exposed to the agent. Suicide genes are known in the art and include, for example, the Herpes Simplex Virus (HSV) thymidine kinase (TK) gene, cytosine deaminase, purine nucleoside phosphorylase, nitroreductase, and the inducible caspase 9 gene system.

[0104] Another embodiment of the invention further provides a host cell comprising any of the recombinant expression vectors described herein. As used herein, the term "host cell" refers to any type of cell that can contain the inventive recombinant expression vector. The host cell can be a eukaryotic cell, e.g., plant, animal, fungi, or algae, or can be a prokaryotic cell, e.g., bacteria or protozoa. The host cell can be a cultured cell or a primary cell, i.e., isolated directly from an organism, e.g., a human or mouse. The host cell can be an adherent cell or a suspended cell, i.e., a cell that grows in suspension. Suitable host cells are known in the art and include, for instance, DH5α *E. coli* cells, Chinese hamster ovarian cells, monkey VERO cells, COS cells, HEK293 cells, and the like. For purposes of amplifying or replicating the recombinant expression vector, the host cell is preferably a prokaryotic cell, e.g., a DH5α cell. For purposes of producing a recombinant TCR, polypeptide, or protein, the host cell is preferably a mammalian cell. Most preferably, the host cell is a human cell. While the host cell can be of any cell type, can originate from any type of tissue, and can be of any developmental stage, the host cell preferably is a peripheral blood lymphocyte (PBL) or a peripheral blood mononuclear cell (PBMC). More preferably, the host cell is a T cell. In an embodiment of the invention, the host cell is a human lymphocyte. In another embodiment of the invention, the host cell is selected from a T cell, a natural killer T (NKT) cell, an invariant natural killer T (iNKT) cell, and a natural killer (NK) cell. Still another embodiment of the invention provides a method of producing a host cell expressing a TCR that has antigenic specificity for the peptide of VVVGA**D**GVGK (SEQ ID NO: 29), the method comprising contacting a cell with any of the vectors described herein under conditions that allow introduction of the vector into the cell.

[0105] For purposes herein, the T cell can be any T cell, such as a cultured T cell, e.g., a primary T cell, or a T cell from a cultured T cell line, e.g., Jurkat, SupT1, etc., or a T cell obtained from a mammal. If obtained from a mammal, the T cell can be obtained from numerous sources, including but not limited to blood, bone marrow, lymph node, the thymus, or other tissues or fluids. T cells can also be enriched for or purified. Preferably, the T cell is a human T cell. The T cell can be any type of T cell and can be of any developmental stage, including but not limited to, $CD4^+/CD8^+$ double positive T cells, $CD4^+$ helper T cells, e.g., Th_1 and Th_2 cells, $CD4^+$ T cells, $CD8^+$ T cells (e.g., cytotoxic T cells), tumor infiltrating lymphocytes (TILs), memory T cells (e.g., central memory T cells and effector memory T cells), naïve T cells, and the like.

[0106] Also provided by the invention is a population of cells comprising at least one host cell described herein. The population of cells can be a heterogeneous population comprising the host cell comprising any of the recombinant expression vectors described, in addition to at least one other cell, e.g., a host cell (e.g., a T cell), which does not comprise any of the recombinant expression vectors, or a cell other than a T cell, e.g., a B cell, a macrophage, a neutrophil, an erythrocyte, a hepatocyte, an endothelial cell, an epithelial cell, a muscle cell, a brain cell, etc. Alternatively, the population of cells can be a substantially homogeneous population, in which the population comprises mainly of host cells (e.g., consisting essentially of) comprising the recombinant expression vector. The population also can be a clonal population of cells, in which all cells of the population are clones of a single host cell comprising a recombinant expression vector, such that all cells of the population comprise the recombinant expression vector. In one embodiment of the invention, the population of cells is a clonal population comprising host cells comprising a recombinant expression vector as described herein.

[0107] In an embodiment of the invention, the numbers of cells in the population may be rapidly expanded. Expansion of the numbers of T cells can be accomplished by any of a number of methods as are known in the art as described in, for example, U.S. Patent 8,034,334; U.S. Patent 8,383,099; U.S. Patent Application Publication No. 2012/0244133; Dudley et al., *J. Immunother.*, 26:332-42 (2003); and Riddell et al., *J. Immunol. Methods*, 128:189-201 (1990). In an embodiment, expansion of the numbers of T cells is carried out by culturing the T cells with OKT3 antibody, IL-2, and feeder PBMC (e.g., irradiated allogeneic PBMC).

[0108] The inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, and host cells (including populations thereof), can be isolated and/or purified. The term "isolated," as used herein, means having been removed from its natural environment. The term "purified," as used herein, means having been increased in purity, wherein "purity" is a relative term, and not to be necessarily construed as absolute purity. For example, the purity can be at least about 50%, can be greater than about 60%, about 70%, about 80%, about 90%, about 95%, or can be about 100%.

[0109] The inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, and host cells (including populations thereof), all of which are collectively referred to as "inventive TCR materials" hereinafter, can be formulated into a composition, such as a pharmaceutical composition. In this regard, the invention provides a pharmaceutical composition comprising any of the TCRs, polypeptides, proteins, nucleic acids, expression vectors, and host cells (including populations thereof), described herein, and a pharmaceutically acceptable carrier. The inventive pharmaceutical compositions containing any of the inventive TCR materials can comprise more than one inventive TCR material, e.g., a polypeptide and a nucleic acid, or two or more different TCRs. Alternatively, the pharmaceutical composition can comprise an inventive TCR material in combination with another pharmaceutically active agent(s) or drug(s), such as a chemotherapeutic agent, e.g., asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, vincristine, etc.

[0110] Preferably, the carrier is a pharmaceutically acceptable carrier. With respect to pharmaceutical compositions, the carrier can be any of those conventionally used for the particular inventive TCR material under consideration. Methods for preparing administrable compositions are known or apparent to those skilled in the art and are described in more detail in, for example, *Remington: The Science and Practice of Pharmacy*, 22nd Ed., Pharmaceutical Press (2012). It is preferred that the pharmaceutically acceptable carrier be one which has no detrimental side effects or toxicity under the conditions of use.

[0111] The choice of carrier will be determined in part by the particular inventive TCR material, as well as by the particular method used to administer the inventive TCR material. Accordingly, there are a variety of suitable formulations of the pharmaceutical composition of the invention. Suitable formulations may include any of those for parenteral, subcutaneous, intravenous, intramuscular, intraarterial, intrathecal, intratumoral, or interperitoneal administration. More than one route can be used to administer the inventive TCR materials, and in certain instances, a particular route can provide a more immediate and more effective response than another route.

[0112] Preferably, the inventive TCR material is administered by injection, e.g., intravenously. When the inventive TCR material is a host cell (or population thereof) expressing the inventive TCR, the pharmaceutically acceptable carrier for the cells for injection may include any isotonic carrier such as, for example, normal saline (about 0.90% w/v of NaCl in water, about 300 mOsm/L NaCl in water, or about 9.0 g NaCl per liter of water), NORMOSOL R electrolyte solution (Abbott, Chicago, IL), PLASMA-LYTE A (Baxter, Deerfield, IL), about 5% dextrose in water, or Ringer's lactate. In an embodiment, the pharmaceutically acceptable carrier is supplemented with human serum albumin.

[0113] For purposes of the invention, the amount or dose (e.g., numbers of cells when the inventive TCR material is one or more cells) of the inventive TCR material administered should be sufficient to effect, e.g., a therapeutic or prophylactic response, in the subject or animal over a reasonable time frame. For example, the dose of the inventive TCR material should be sufficient to bind to a cancer antigen (e.g., G12D RAS), or detect, treat or prevent cancer in a period of from about 2 hours or longer, e.g., 12 to 24 or more hours, from the time of administration. In certain embodiments, the time period could be even longer. The dose will be determined by the efficacy of the particular inventive TCR material and the condition of the animal (e.g., human), as well as the body weight of the animal (e.g., human) to be treated.

[0114] Many assays for determining an administered dose are known in the art. For purposes of the invention, an assay, which comprises comparing the extent to which target cells are lysed or IFN-γ is secreted by T cells expressing the inventive TCR, polypeptide, or protein upon administration of a given dose of such T cells to a mammal among a set of mammals of which each is given a different dose of the T cells, could be used to determine a starting dose to be administered to a mammal. The extent to which target cells are lysed or IFN-γ is secreted upon administration of a certain dose can be assayed by methods known in the art.

[0115] The dose of the inventive TCR material also will be determined by the existence, nature and extent of any adverse side effects that might accompany the administration of a particular inventive TCR material. Typically, the attending physician will decide the dosage of the inventive TCR material with which to treat each individual patient, taking into consideration a variety of factors, such as age, body weight, general health, diet, sex, inventive TCR material to be administered, route of administration, and the severity of the cancer being treated. In an embodiment in which the inventive TCR material is a population of cells, the number of cells administered per infusion may vary, e.g., from about 1 x 10^6 to about 1 x 10^{12} cells or more. In certain embodiments, fewer than 1 x 10^6 cells may be administered.

[0116] One of ordinary skill in the art will readily appreciate that the inventive TCR materials of the invention can be modified in any number of ways, such that the therapeutic or prophylactic efficacy of the inventive TCR materials is increased through the modification. For instance, the inventive TCR materials can be conjugated either directly or indirectly through a bridge to a chemotherapeutic agent. The practice of conjugating compounds to a chemotherapeutic agent is known in the art. One of ordinary skill in the art recognizes that sites on the inventive TCR materials, which are not necessary for the function of the inventive TCR materials, are suitable sites for attaching a bridge and/or a chemotherapeutic agent, provided that the bridge and/or chemotherapeutic agent, once attached to the inventive TCR materials, do(es) not interfere with the function of the inventive TCR materials, i.e., the ability to bind to G12D RAS or to detect, treat, or prevent cancer.

[0117] It is contemplated that the inventive pharmaceutical compositions, TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, and populations of cells can be used in methods of treating or preventing cancer. Without being bound to a particular theory, the inventive TCRs are believed to bind specifically to G12D RAS, such that the TCR (or related inventive polypeptide or protein), when expressed by a cell, is able to mediate an immune response against a target cell expressing G12D RAS. In this regard, an embodiment of the invention provides a method of treating or preventing cancer in a mammal, comprising administering to the mammal any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, in an amount effective to treat or prevent cancer in the mammal.

[0118] An embodiment of the invention provides a method of inducing an immune response against a cancer in a mammal, comprising administering to the mammal any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, or proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, in an amount effective to induce an immune response against the cancer in the mammal.

[0119] An embodiment of the invention provides any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, for use in the treatment or prevention of cancer in a mammal.

[0120] An embodiment of the invention provides any of the pharmaceutical compositions, TCRs, polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the TCRs, polypeptides, or proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the TCRs, polypeptides, or proteins described herein, for use in inducing an immune response against a cancer in a mammal.

[0121] The terms "treat," and "prevent" as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment or prevention. Rather, there are varying degrees of treatment or prevention of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment or prevention of cancer in a mammal. Furthermore, the treatment or prevention provided by the inventive method can include treatment or prevention of one or more conditions or symptoms of the cancer being treated or prevented. For example, treatment or prevention can include promoting the regression of a tumor. Also, for purposes herein, "prevention" can encompass delaying the onset of the cancer, or a symptom or condition thereof. Alternatively or additionally, “prevention” may encompass preventing or delaying the recurrence of cancer, or a symptom or condition thereof.

[0122] Also provided is a method of detecting the presence of cancer in a mammal. The method comprises (i) contacting a sample comprising one or more cells from the mammal with any of the inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, populations of cells, or pharmaceutical compositions described herein, thereby forming a complex, and (ii) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal.

[0123] With respect to the inventive method of detecting cancer in a mammal, the sample of cells can be a sample comprising whole cells, lysates thereof, or a fraction of the whole cell lysates, e.g., a nuclear or cytoplasmic fraction, a whole protein fraction, or a nucleic acid fraction.

[0124] For purposes of the inventive method of detecting cancer, the contacting can take place *in vitro* or *in vivo* with respect to the mammal. Preferably, the contacting is *in vitro.*

[0125] Also, detection of the complex can occur through any number of ways known in the art. For instance, the inventive TCRs, polypeptides, proteins, nucleic acids, recombinant expression vectors, host cells, or populations of cells, described herein, can be labeled with a detectable label such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles).

[0126] For purposes of the inventive methods, wherein host cells or populations of cells are administered, the cells can be cells that are allogeneic or autologous to the mammal. Preferably, the cells are autologous to the mammal.

[0127] With respect to the inventive methods, the cancer can be any cancer, including, e.g., any of acute lymphocytic cancer, acute myeloid leukemia, alveolar rhabdomyosarcoma, bone cancer, brain cancer, breast cancer, cancer of the anus, anal canal, or anorectum, cancer of the eye, cancer of the intrahepatic bile duct, cancer of the joints, cancer of the neck, gallbladder, or pleura, cancer of the nose, nasal cavity, or middle ear, cancer of the oral cavity, cancer of the vagina, cancer of the vulva, chronic lymphocytic leukemia, chronic myeloid cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, uterine cervical cancer, gastrointestinal carcinoid tumor, glioma, Hodgkin lymphoma, hypopharynx cancer, kidney cancer, larynx cancer, liver cancer, lung cancer, malignant mesothelioma, melanoma, multiple myeloma, nasopharynx cancer, non-Hodgkin lymphoma, cancer of the oropharynx, ovarian cancer, cancer of the penis, pancreatic cancer, peritoneum, omentum, and mesentery cancer, pharynx cancer, prostate cancer, rectal cancer, renal cancer, skin cancer, small intestine cancer, soft tissue cancer, stomach cancer, testicular cancer, thyroid cancer, cancer of the uterus, ureter cancer, and urinary bladder cancer. A preferred cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer. Preferably, the lung cancer is lung adenocarcinoma, the ovarian cancer is epithelial ovarian cancer, and the pancreatic cancer is pancreatic adenocarcinoma. In an embodiment of the invention, the cancer expresses a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid, wherein the mutated human RAS amino acid sequence is a mutated human KRAS, a mutated human HRAS, or a mutated human NRAS amino acid sequence, and wherein position 12 is defined by reference to the WT human KRAS, WT human HRAS, or WT human NRAS protein, respectively. The mutated human KRAS, mutated human HRAS, and mutated human NRAS expressed by the cancer may be as described herein with respect to other aspects of the invention.

[0128] The mammal referred to in the inventive methods can be any mammal. As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits. It is preferred that the mammals are from the order Carnivora, including Felines (cats) and Canines (dogs). It is more preferred that the mammals are from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human.

[0129] It shall be noted that the preceding are merely examples of embodiments. Other exemplary embodiments are apparent from the entirety of the description herein. It will also be understood by one of ordinary skill in the art that each of these embodiments may be used in various combinations with the other embodiments provided herein.

[0130] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0131] This example demonstrates the isolation of a TCR having antigenic specificity for human KRAS with the G12D mutation.

[0132] The endometrial cancer of Patient 4373 progressed following treatment with autologous PBL transduced with a murine TCR having antigenic specificity for HLA-A11 restricted, human KRAS G12D. The patient’s TIL were screened for reactivity to KRAS G12D, as follows. TIL from tumor fragment numbers F4, F5, F6, F8, F9, and F10 were co-cultured with the following target cells:

- 4373 Autologous DC mRNA transfected with a tandem minigene (TMG) encoding the wild-type (WT) KRAS TMG peptide

MTEYKLVVVGAGGVGKSALTIQLIMTEYKLVVVGAGGVGKSALTIQLIQETCLLDILDTAGQEEYSAMRDQYMR (SEQ ID NO: 48);

- 4373 Autologous DC mRNA transfected with a TMG encoding the mutated (Mut) KRAS peptide: MTEYKLVVVGADGVGKSALTIQLIMTEYKLVVVGAVGVGKSALTIQLIMTEYKLVVVGACGVGKSALTIQLIMTEYKLVVVGAAGVGKSALTIQLIMTEYKLVVVGASGVGKSALTIQLIMTEYKLVVVGAGDVGKSALTIQLIQMTEYKLVVVGAGRVGKSALTIQLIQMTEYKLVVVGAGVVGKSALTIQLIQETCLLDILDTAGREEYSAMRDQYMRETCLLDILDTAGLEEYSAMRDQYMRETCLLDILDTAGKEEYSAMRDQYMRETCLLDILDTAGHEEYSAMRDQYMR (SEQ ID NO: 49);
- G12 WT KRAS long peptide (LP) (MTEYKLVVVGA**G**GVGKSALTIQLI) (SEQ ID NO: 27);
- G12D Mut KRAS LP (MTEYKLVVVGA**D**GVGKSALTIQLI) (SEQ ID NO: 26); or
- minimal KRAS epitope (ME) A11 (G12D 9mer + 10mer) VVGA**D**GVGK + VVVGA**D**GVGK (SEQ ID NO: 28 and 29).

[0133] As controls, the transduced cells were cultured alone (TIL only) or co-cultured with dimethyl sulfoxide (DMSO) or anti-CD3/anti-CD28 Dynabeads material.

[0134] Interferon-gamma (IFN-γ) secretion following-co-culture was measured by enzyme-linked immune absorbent spot (ELISpot). The results are shown in Figure 1A. The percentage of cells expressing 4-1BB and OX40 was measured by flow cytometry assay. The results are shown in Figure 1B. As shown in Figures 1A-1B, TIL with anti-G12D reactivity were detected in tumor fragment F8.

[0135] TIL from tumor fragment F8 were separated into single cell samples. A TCR with antigenic specificity for human KRAS with the G12D mutation presented by HLA-A11 was isolated from the TIL. To sequence the reactive 4373 TCR, the reactive TIL were sorted by fluorescence-activated cell sorting (FACS) based on the upregulation of the T cell activation marker, 4-1BB. Subsequently, the cells were lysed, and the TCR transcripts were Sanger sequenced. The amino acid sequences of the 4373 TCR α and β chain variable regions are shown in Table 5. The CDRs are underlined.

TABLE 5

TCR Name	TCR chain	Amino acid sequence
4373 TCR	Alpha chain variable region (TRAV23/DV6*01 or TRAV23/DV6*02 or TRAV23/DV6*03 or TRAV23/DV6*04 + TRAJ18*01) (with wild type N-terminal signal peptide)	MDKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAEAGNHRGSTLGRLYFGRGTQLTVWP (SEQ ID NO: 7)
	Alpha chain variable region (TRAV23/DV6*01 or TRAV23/DV6*02 or TRAV23/DV6*03 or TRAV23/DV6*04 + TRAJ18*01) (with variant N-terminal signal peptide)	MAKILGASFLVLWLQLCWVSGQQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAEAGNHRGSTLGRLYFGRGTQLTVWP (SEQ ID NO: 51)
	Beta chain variable region (TRBV5-1*01 + TRBJ2-1*01) (with variant N-terminal signal peptide)	MASRLLCWVLLCLLGAGPVKAGVTQTPRYLIKTRGQQVTLSCSPISGHRSVSWYQQTPGQGLQFLFEYFSETQRNKGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYLCASSLAAGGYFNEQFFGPGTRLTVL (SEQ ID NO: 8)
	Beta chain variable region (TRBV5-1*01 + TRBJ2-1*01) (with wild type N-terminal signal peptide)	MGSRLLCWVLLCLLGAGPVKAGVTQTPRYLIKTRGQQVTLSCSPISGHRSVSWYQQTPGQGLQFLFEYFSETQRNKGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYLCASSLAAGGYFNEQFFGPGTRLTVL (SEQ ID NO: 52)
	Alpha (TRAV23/DV6*01 or	QQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAEAGNHRGSTLGRLYFGRGTQLTVWP

TCR Name	TCR chain	Amino acid sequence
	TRAV23/DV6*02 or TRAV23/DV6*03 or TRAV23/DV6*04 + TRAJ18*01) (IMGT predicted sequence without N-terminal signal peptide)	(SEQ ID NO: 32)
	Beta (TRBV5-1*01 + TRBJ2-1*01) (IMGT predicted sequence without N-terminal signal peptide)	KAGVTQTPRYLIKTRGQQVTLSCSPISGHRSVSWYQQTPGQGLQFLFEYFSETQRNKGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYLCASSLAAGGYFNEQFFGPGTRLTVL (SEQ ID NO: 33)
	Alpha (TRAV23/DV6*01 or TRAV23/DV6*02 or TRAV23/DV6*03 or TRAV23/DV6*04 + TRAJ18*01) (SignalP predicted sequence without N-terminal signal peptide)	QQKEKSDQQQVKQSPQSLIVQKGGISIINCAYENTAFDYFPWYQQFPGKGPALLIAIRPDVSEKKEGRFTISFNKSAKQFSLHIMDSQPGDSATYFCAAEAGNHRGSTLGRLYFGRGTQLTVWP (SEQ ID NO: 59)
	Beta (TRBV5-1*01 + TRBJ2-1*01) (SignalP predicted sequence without N-terminal signal peptide)	GVTQTPRYLIKTRGQQVTLSCSPISGHRSVSWYQQTPGQGLQFLFEYFSETQRNKGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYLCASSLAAGGYFNEQFFGPGTRLTVL (SEQ ID NO: 60)

EXAMPLE 2

[0136] This example demonstrates a method of preparing a retroviral vector comprising a nucleotide sequence encoding the human anti-G12D TCR of Example 1 with modified murine constant regions.

[0137] A nucleic acid sequence encoding the human G12D RAS-reactive 4373 TCR of Example 1 and including a cysteine substituted, LVL-modified murine constant region was cloned into a retroviral expression vector. The α chain murine constant region comprised the amino acid sequence of SEQ ID NO: 17 wherein X at position 48 is Cys, X at position 112 is Leu, X at position 114 is Ile, and X at position 115 is Val (SEQ ID NO:38). The resulting full-length α chain comprised the amino acid sequence of SEQ ID NO: 40. The β chain constant region comprised the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 is Cys (SEQ ID NO:39). The resulting full-length β chain comprised the amino acid sequence of SEQ ID NO: 41. A linker comprising the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 25) was positioned between the α chain constant region and the β chain variable region. The vector comprised an expression cassette comprising the nucleotide sequence of SEQ ID NO: 46 (codon optimized nucleotide sequence encoding, from the 5' end to 3' end: TCR β chain, linker, TCR α chain), which encoded the amino acid sequence of SEQ ID NO: 47 (amino acid sequence comprising, from the amino terminus to the carboxyl terminus, TCR β chain, linker, TCR α chain).

EXAMPLE 3

[0138] This example demonstrates that the anti-G12D TCR of Example 2 (with human variable regions) provides the same or better reactivity as the murine anti-G12D TCR of Example 1.

[0139] Patient 4373's CD8+ autologous PBL were transduced with the retroviral expression vector encoding (i) the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions) (also referred to herein as "TCR2"), (ii) a second TCR (referred to herein as "TCR1", which was also obtained by single-cell sequencing the reactive TIL shown in Figure 1 or (iii) the HLA-A11 restricted, murine anti-KRAS G12D TCR of Example 1 (control). The reactivity of CD8+ transduced cells was tested following co-culture with the following target cells:

- COS HLA-A2 transduced cells,
- COS HLA-A2-G12 WT KRAS cell line,
- COS HLA-A11 transduced cells,
- COS HLA-A11-G12D cell line, or

- T cells only (no target cells) (-).

[0140] The percentage of cells expressing 4-1BB and OX40 following co-culture with target cells was measured. The results are shown in Figure 2. The transduced cells also underwent HLA-A11 minimal epitope titration experiments.

[0141] In a separate experiment, Patient 4373's autologous CD8+ PBL were transduced with the retroviral expression vector encoding (i) the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions), (ii) TCR1, (iii) the HLA-A11 restricted, murine anti-KRAS G12D TCR of Example 1, or (iv) GFP. Cells transduced with an empty vector ("Mock Td" (Td=Transduction)) served as an additional control. The reactivity of CD8+ transduced cells was tested following co-culture with the following target cells:

- autologous dendritic cells (DC) transduced with full length (FL) WT KRAS gene;
- autologous DC transduced with FL KRAS gene with G12D mutation;
- autologous DC transduced with WT KRAS LP (MTEYKLVVVGA**G**GVGKSALTIQLI) (SEQ ID NO: 27);
- autologous DC transduced with G12D Mut KRAS LP (MTEYKLVVVGA**D**GVGKSALTIQLI) (SEQ ID NO: 26);
- minimal KRAS epitope (ME) A02 WT;
- ME A02 G12D KLVVVGADGV (SEQ ID NO: 50);
- ME HLA-A11 WT mix (mixture of the peptides of WT 9-mer SEQ ID NO: 30 and WT 10-MER SEQ ID NO: 31); or

- ME HLA-A11 G12D mix (mixture of the peptides of G12D 9-mer SEQ ID NO: 28 and G12D 10-MER SEQ ID NO: 29).

[0142] As a control, the transduced cells were cultured alone (T cells only) or were co-cultured with DMSO or anti-CD28/anti-CD3 DYNABEADS material. IFN-γ secretion was measured by ELISpot. The results are shown in Figure 3A and Table 6. The percentage of cells expressing 4-1BB and OX40 was measured. The results are shown in Figure 3B.

TABLE 6

	4373 TCR1	**4373 TCR2**	**mTCR (G12D-A11)**
FL WT	178	232	164
FL G12D	232	1095	976
LP WT	144	186	205
LP G12D	184	1223	1143
ME A*02 WT	167	200	196
ME A*02 G12D	157	234	188
ME A*11 WT mix	201	217	211
ME A*11 G12D mix	203	1371	1373
DMSO	168	253	194
T Cell only	186	187	219
CD3/CD28 Dynabeads	1032	1022	1155

[0143] In a separate experiment, Patient 4373's autologous PBL were transduced with the retroviral expression vector encoding (i) the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions) or (ii) the HLA-A11 restricted, murine anti-KRAS G12D TCR of Example 1.

[0144] Autologous DCs were loaded with the following peptides at the concentrations shown in Table 7: a mutated minimal epitope (ME) peptide with 9 amino acid residues (VVGA**D**GVGK) (SEQ ID NO: 28), a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29), a WT minimal epitope peptide with 9 amino acid residues (VVGA**G**GVGK) (SEQ ID NO: 30), or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). IFN-γ secretion was measured by ELISpot. The results are shown in Table 7.

TABLE 7

A11 – ME peptide loaded DC			**10000 ng**	**1000ng**	**100 ng**	**10 ng**	**1 ng**	**0.1 ng**	**0.01 ng**
	ME 9mer	WT	224	256	220	228	228	204	212

A11 – ME peptide loaded DC			**10000 ng**	**1000ng**	**100 ng**	**10 ng**	**1 ng**	**0.1 ng**	**0.01 ng**
mTCR		G12D	235	236	255	289	243	249	267
	ME 10mer	WT	254	229	256	228	231	258	262
		G12D	1349	1096	735	401	292	288	234
4373 TCR2	ME 9mer	WT	282	277	300	284	275	286	253
		G12D	515	308	272	290	266	301	286
	ME 10mer	WT	273	256	237	251	282	293	275
		G12D	1532	1395	1037	495	298	264	245

[0145] As shown in Figures 2-3B and Tables 6-7, the anti-G12D TCR of Example 2 (with human variable regions) provided the same or better reactivity as the murine anti-G12D TCR of Example 1.

EXAMPLE 4

[0146] This example demonstrates that PBL transduced with the anti-G12D TCR of Example 2 (with human variable regions) specifically recognizes HLA-A11-restricted G12D with high avidity.

[0147] Patient 4373's autologous PBL were transduced with the retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions).

[0148] Autologous DCs were loaded with the following peptides at the concentrations shown in Figure 4A: a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). IFN-γ secretion was measured by ELISpot. The results are shown in Figure 4A.

EXAMPLE 5

[0149] This example demonstrates that CD8+ PBL transduced with the anti-G12D TCR of Example 2 (with human variable regions) specifically recognizes HLA-A11-restricted G12D with high avidity.

[0150] Patient 4373's autologous CD8+ PBL were transduced with the retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions).

[0151] Autologous DCs were loaded with the following peptides at the concentrations shown in Figure 4B: a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). The expression of 4-1BB and OX40 was measured by FACS. The results are shown in Figure 4B.

EXAMPLE 6

[0152] This example demonstrates that CD4+ PBL transduced with the anti-G12D TCR of Example 2 (with human variable regions) specifically recognizes HLA-A11-restricted G12D with high avidity.

[0153] Patient 4373's autologous CD4+ PBL were transduced with the retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions).

[0154] Autologous DCs were loaded with the following peptides at the concentrations shown in Figure 4C: a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). The expression of 4-1BB and OX40 was measured by FACS. The results are shown in Figure 4C.

EXAMPLE 7

[0155] This example demonstrates that CD8+ PBL transduced with the anti-G12D TCR of Example 2 (with human variable regions) specifically recognizes HLA-A11-restricted G12D with high avidity.

[0156] Patient 4373's autologous CD8+ PBL were transduced with the retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions).

[0157] COS cells were loaded with the following peptides at the concentrations shown in Figure 5A: a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). IFN-γ secretion was measured by ELISpot. The results are shown in Figure 5A.

EXAMPLE 8

[0158] This example demonstrates that CD8+ PBL transduced with the anti-G12D TCR of Example 2 (with human variable regions) specifically recognizes HLA-A11-restricted G12D with high avidity.

[0159] Patient 4373's autologous CD8+ PBL were transduced with the retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions).

[0160] COS cells were transduced with HLA-A11 and loaded with the following peptides at the concentrations shown in Figure 5B: a mutated minimal epitope peptide with 10 amino acid residues (VVVGA**D**GVGK) (SEQ ID NO: 29) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). The expression of 4-1BB and OX40 was measured by FACS. The results are shown in Figure 5B.

EXAMPLE 9

[0161] This example demonstrates that CD4+ PBL transduced with the anti-G12D TCR of Example 2 (with human variable regions) specifically recognizes HLA-A11-restricted G12D with high avidity.

[0162] Patient 4373's autologous CD4+ PBL were transduced with the retroviral expression vector encoding the G12D RAS-reactive 4373 TCR of Example 2 (with human variable regions).

[0163] COS cells were loaded with the following peptides at the concentrations shown in Figure 5C: a mutated minimal epitope peptide with 10 amino acid residues

(VVVGA**D**GVGK) (SEQ ID NO: 29) or a WT minimal epitope peptide with 10 amino acid residues (VVVGA**G**GVGK) (SEQ ID NO: 31). The expression of 4-1BB and OX40 was measured by FACS. The results are shown in Figure 5C.

[0164] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0165] The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0166] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIMS:

1. An isolated or purified T-cell receptor (TCR) comprising all of the amino acid sequences of SEQ ID NOs: 1-3, 4-6, or 1-6, wherein the TCR has antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid,

wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS), a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS), or a mutated human Neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence, and

wherein position 12 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS protein, respectively.

2. The isolated or purified TCR according to claim 1, wherein the mutated human RAS amino acid sequence is VVVGADGVGK (SEQ ID NO: 29).

3. The isolated or purified TCR according to claim 1 or 2, wherein the TCR does not have antigenic specificity for the wild-type human RAS amino acid sequence of VVVGAGGVGK (SEQ ID NO: 31).

4. The isolated or purified TCR according to any one of claims 1-3, wherein the mutated human RAS amino acid sequence is presented by a human leukocyte antigen (HLA) Class I molecule.

5. The isolated or purified TCR according to claim 4, wherein the HLA Class I molecule is an HLA-A molecule.

6. The isolated or purified TCR according to claim 4, wherein the HLA Class I molecule is an HLA-A11 molecule.

7. The isolated or purified TCR according to claim 4, wherein the HLA Class I molecule is encoded by the HLA-A*11:01 allele.

8. The isolated or purified TCR according to any one of claims 1-7, comprising:

(i) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 7;

(ii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8;

(iii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 51;

(iv) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 52;

(v) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 32;

(vi) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 33;

(vii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 59;

(viii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 60; or

(ix) both (i) and (ii), both (i) and (iv), both (ii) and (iii), both (iii) and (iv), both (v) and (vi), both (v) and (viii), both (vi) and (vii), or both (vii) and (viii).

9. The isolated or purified TCR according to any one of claims 1-8, comprising:

(i) the amino acid sequence of SEQ ID NO: 7;

(ii) the amino acid sequence of SEQ ID NO: 8;

(iii) the amino acid sequence of SEQ ID NO: 51;

(iv) the amino acid sequence of SEQ ID NO: 52;

(v) the amino acid sequence of SEQ ID NO: 32;

(vi) the amino acid sequence of SEQ ID NO: 33;

(vii) the amino acid sequence of SEQ ID NO: 59;

(viii) the amino acid sequence of SEQ ID NO: 60; or

(ix) both (i) and (ii), both (i) and (iv), both (ii) and (iii), both (iii) and (iv), both (v) and (vi), both (v) and (viii), both (vi) and (vii), or both (vii) and (viii).

10. The isolated or purified TCR according to any one of claims 1-9, further comprising:

(a) an α chain constant region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain constant region comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

(c) both (a) and (b).

11. The isolated or purified TCR according to any one of claims 1-10, further comprising:

(a) an α chain constant region comprising the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain constant region comprising the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

(c) both (a) and (b).

12. The isolated or purified TCR according to any one of claims 1-11, comprising:

(a) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys;

(c) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 53, wherein:

(i) X at position 193 of SEQ ID NO: 53 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys;

(e) both (a) and (b), both (a) and (d), both (b) and (c), or both (c) and (d);

(f) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 165 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(g) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys;

(h) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 61, wherein:

(i) X at position 172 of SEQ ID NO: 61 is Thr or Cys;

(ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(i) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;

(j) both (f) and (g), or both (h) and (i);

(k) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 36;

(l) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 37;

(m) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 63;

(n) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 64;

(o) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 42;

(p) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 43;

(q) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 65;

(r) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 66;

(s) both (k) and (l), both (m) and (n), both (o) and (p), or both (q) and (r);

(t) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 23;

(u) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 24;

(v) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 55;

(w) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 56;

(x) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 40;

(y) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 41;

(z) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 57;

(aa) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 58; or

(ab) both (t) and (u), both (t) and (w), both (u) and (v), both (v) and (w), both (x) and (y), both (x) and (aa), both (y) and (z), or both (z) and (aa).

13. The isolated or purified TCR according to any one of claims 1-12, comprising:

(a) an α chain comprising the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain comprising the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys;

(c) an α chain comprising the amino acid sequence of SEQ ID NO: 53, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys;

(e) both (a) and (b), both (a) and (d), both (b) and (c), or both (c) and (d);

(f) an α chain comprising the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 165 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(g) a β chain comprising the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys;

(h) an α chain comprising the amino acid sequence of SEQ ID NO: 61, wherein:

(i) X at position 172 of SEQ ID NO: 61 is Thr or Cys;

(ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(i) a β chain comprising the amino acid sequence of SEQ ID NO: 62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;

(j) both (f) and (g), or both (h) and (i);

(k) an α chain comprising the amino acid sequence of SEQ ID NO: 36;

(l) a β chain comprising the amino acid sequence of SEQ ID NO: 37;

(m) an α chain comprising the amino acid sequence of SEQ ID NO: 63;

(n) a β chain comprising the amino acid sequence of SEQ ID NO: 64;

(o) an α chain comprising the amino acid sequence of SEQ ID NO: 42;

(p) a β chain comprising the amino acid sequence of SEQ ID NO: 43;

(q) an α chain comprising the amino acid sequence of SEQ ID NO: 65;

(r) a β chain comprising the amino acid sequence of SEQ ID NO: 66;

(s) both (k) and (l), both (m) and (n), both (o) and (p), or both (q) and (r);

(t) an α chain comprising the amino acid sequence of SEQ ID NO: 23;

(u) a β chain comprising the amino acid sequence of SEQ ID NO: 24;

(v) an α chain comprising the amino acid sequence of SEQ ID NO: 55;

(w) a β chain comprising the amino acid sequence of SEQ ID NO: 56;

(x) an α chain comprising the amino acid sequence of SEQ ID NO: 40;

(y) a β chain comprising the amino acid sequence of SEQ ID NO: 41;

(z) an α chain comprising the amino acid sequence of SEQ ID NO: 57;

(aa) a β chain comprising the amino acid sequence of SEQ ID NO: 58; or

(ab) both (t) and (u), both (t) and (w), both (u) and (v), both (v) and (w), both (x) and (y), both (x) and (aa), both (y) and (z), or both (z) and (aa).

14. An isolated or purified polypeptide comprising a functional portion of the TCR according to any one of claims 1-13, wherein the functional portion comprises the amino acid sequences of:

(a) all of SEQ ID NOs: 1-3,

(b) all of SEQ ID NOs: 4-6, or

(c) all of SEQ ID NOs: 1-6.

15. The isolated or purified polypeptide according to claim 14, wherein the functional portion comprises:

(i) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 7;

(ii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8;

(iii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 51;

(iv) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 52;

(v) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 32;

(vi) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 33;

(vii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 59;

(viii) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 60; or

(ix) both (i) and (ii), both (i) and (iv), both (ii) and (iii), both (iii) and (iv), both (v) and (vi), both (v) and (viii), both (vi) and (vii), or both (vii) and (viii).

16. The isolated or purified polypeptide according to claim 14 or 15, wherein the functional portion comprises the amino acid sequence(s) of:

(i) SEQ ID NO: 7;

(ii) SEQ ID NO: 8;

(iii) SEQ ID NO: 51;

(iv) SEQ ID NO: 52;

(v) SEQ ID NO: 32;

(vi) SEQ ID NO: 33;

(vii) SEQ ID NO: 59;

(viii) SEQ ID NO: 60; or

(ix) both (i) and (ii), both (i) and (iv), both (ii) and (iii), both (iii) and (iv), both (v) and (vi), both (v) and (viii), both (vi) and (vii), or both (vii) and (viii).

17. The isolated or purified polypeptide according to any one of claims 14-16, further comprising:

(a) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

(c) both (a) and (b).

18. The isolated or purified polypeptide according to any one of claims 14-17, further comprising:

(a) the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

(c) both (a) and (b).

19. The isolated or purified polypeptide according to any one of claims 14-18, comprising:

(a) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys;

(c) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 53, wherein:

(i) X at position 193 of SEQ ID NO: 53 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys;

(e) both (a) and (b), both (a) and (d), both (b) and (c), or both (c) and (d);

(f) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 165 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(g) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys;

(h) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 61, wherein:

(i) X at position 172 of SEQ ID NO: 61 is Thr or Cys;

(ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(i) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;

(j) both (f) and (g), or both (h) and (i);

(k) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 36;

(l) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 37;

(m) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 63;

(n) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 64;

(o) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 42;

(p) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 43;

(q) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 65;

(r) a a β chain comprising n amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 66;

(s) both (k) and (l), both (m) and (n), both (o) and (p), or both (q) and (r);

(t) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 23;

(u) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 24;

(v) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 55;

(w) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 56;

(x) an α chain comprising n amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 40;

(y) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 41;

(z) an α chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 57;

(aa) a β chain comprising an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 58; or (ab) both (t) and (u), both (t) and (w), both (u) and (v), both (v) and (w), both (x) and (y), both (x) and (aa), both (y) and (z), or both (z) and (aa).

20. The isolated or purified polypeptide according to any one of claims 14-19, comprising:

(a) an α chain comprising the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) a β chain comprising the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys;

(c) an α chain comprising the amino acid sequence of SEQ ID NO: 53, wherein:

(i) X at position 193 of SEQ ID NO: 53 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) a β chain comprising the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys;

(e) both (a) and (b), both (a) and (d), both (b) and (c), or both (c) and (d);

(f) an α chain comprising the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 165 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(g) a β chain comprising the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys;

(h) an α chain comprising the amino acid sequence of SEQ ID NO: 61, wherein:

(i) X at position 172 of SEQ ID NO: 61 is Thr or Cys;

(ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(i) a β chain comprising the amino acid sequence of SEQ ID NO: 62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;

(j) both (f) and (g), or both (h) and (i);

(k) an α chain comprising the amino acid sequence of SEQ ID NO: 36;

(l) a β chain comprising the amino acid sequence of SEQ ID NO: 37;

(m) an α chain comprising the amino acid sequence of SEQ ID NO: 63;

(n) a β chain comprising the amino acid sequence of SEQ ID NO: 64;

(o) an α chain comprising the amino acid sequence of SEQ ID NO: 42;

(p) a β chain comprising the amino acid sequence of SEQ ID NO: 43;

(q) an α chain comprising the amino acid sequence of SEQ ID NO: 65;

(r) a β chain comprising the amino acid sequence of SEQ ID NO: 66;

(s) both (k) and (l), both (m) and (n), both (o) and (p), or both (q) and (r);

(t) an α chain comprising the amino acid sequence of SEQ ID NO: 23;

(u) a β chain comprising the amino acid sequence of SEQ ID NO: 24;

(v) an α chain comprising the amino acid sequence of SEQ ID NO: 55;

(w) a β chain comprising the amino acid sequence of SEQ ID NO: 56;

(x) an α chain comprising the amino acid sequence of SEQ ID NO: 40;

(y) a β chain comprising the amino acid sequence of SEQ ID NO: 41;

(z) an α chain comprising the amino acid sequence of SEQ ID NO: 57;

(aa) a β chain comprising the amino acid sequence of SEQ ID NO: 58; or

(ab) both (t) and (u), both (t) and (w), both (u) and (v), both (v) and (w), both (x) and (y), both (x) and (aa), both (y) and (z), and both (z) and (aa).

21. An isolated or purified protein, comprising a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 1-3 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 4-6.

22. The isolated or purified protein according to claim 21, wherein

(i) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 7;

(ii) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 8;

(iii) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 51;

(iv) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 52;

(v) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 32;

(vi) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 33;

(vii) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 59;

(viii) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 60; or

(ix) both (i) and (ii), both (i) and (iv), both (ii) and (iii), both (iii) and (iv), both (v) and (vi), both (v) and (viii), both (vi) and (vii), or both (vii) and (viii).

23. The isolated or purified protein according to claim 21 or 22, wherein:

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 7;

(ii) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 8;

(iii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 51;

(iv) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 52;

(v) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 32;

(vi) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 33;

(vii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 59;

(viii) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 60; or

(ix) both (i) and (ii), both (i) and (iv), both (ii) and (iii), both (iii) and (iv), both (v) and (vi), both (v) and (viii), both (vi) and (vii), or both (vii) and (viii).

24. The isolated or purified protein according to any one of claims 21-23, wherein:

(a) the first polypeptide chain further comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the second polypeptide chain further comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

(c) both (a) and (b).

25. The isolated or purified protein according to any one of claims 21-24, wherein:

(a) the first polypeptide chain further comprises the amino acid sequence of SEQ ID NO: 17, wherein:

(i) X at position 48 of SEQ ID NO: 17 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 17 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 17 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 17 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the second polypeptide chain further comprises the amino acid sequence of SEQ ID NO: 18, wherein X at position 57 of SEQ ID NO: 18 is Ser or Cys; or

(c) both (a) and (b).

26. The isolated or purified protein according to any one of claims 21-25, wherein:

(a) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys;

(c) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 53, wherein:

(i) X at position 193 of SEQ ID NO: 53 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 54, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys;

(e) both (a) and (b), both (a) and (d), both (b) and (c), or both (c) and (d);

(f) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 165 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(g) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys;

(h) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 61, wherein:

(i) X at position 172 of SEQ ID NO: 61 is Thr or Cys;

(ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(i) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;

(j) both (f) and (g), or both (h) and (i);

(k) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 36;

(l) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 37;

(m) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 63;

(n) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 64;

(o) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 42;

(p) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 43;

(q) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 65;

(r) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 66;

(s) both (k) and (l), both (m) and (n), both (o) and (p), or both (q) and (r);

(t) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 23;

(u) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 24;

(v) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 55;

(w) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 56;

(x) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 40;

(y) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 41;

(z) the first polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 57;

(aa) the second polypeptide chain comprises an amino acid sequence at least 99% identical to the amino acid sequence of SEQ ID NO: 58; or

(ab) both (t) and (u), both (t) and (w), both (u) and (v), both (v) and (w), both (x) and (y), both (x) and (aa), both (y) and (z), or both (z) and (aa).

27. The isolated or purified protein according to any one of claims 21-26, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 21, wherein:

(i) X at position 193 of SEQ ID NO: 21 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 21 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 21 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 21 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 22, wherein X at position 191 of SEQ ID NO: 22 is Ser or Cys;

(c) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 53, wherein:

(i) X at position 193 of SEQ ID NO: 53 is Thr or Cys;

(ii) X at position 257 of SEQ ID NO: 53 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 259 of SEQ ID NO: 53 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 260 of SEQ ID NO: 53 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(d) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 45, wherein X at position 191 of SEQ ID NO: 54 is Ser or Cys;

(e) both (a) and (b), both (a) and (d), both (b) and (c), or both (c) and (d);

(f) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 34, wherein:

(i) X at position 165 of SEQ ID NO: 34 is Thr or Cys;

(ii) X at position 229 of SEQ ID NO: 34 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 231 of SEQ ID NO: 34 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 232 of SEQ ID NO: 34 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(g) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 35, wherein X at position 172 of SEQ ID NO: 35 is Ser or Cys;

(h) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 61, wherein:

(i) X at position 172 of SEQ ID NO: 61 is Thr or Cys;

(ii) X at position 236 of SEQ ID NO: 61 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 238 of SEQ ID NO: 61 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 239 of SEQ ID NO: 61 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(i) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 62, wherein X at position 170 of SEQ ID NO: 62 is Ser or Cys;

(j) both (f) and (g), or both (h) and (i);

(k) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 36;

(l) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 37;

(m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 63;

(n) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 64;

(o) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 42;

(p) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 43;

(q) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 65;

(r) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 66;

(s) both (k) and (l), both (m) and (n), both (o) and (p), or both (q) and (r);

(t) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 23;

(u) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 24;

(v) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 55;

(w) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 56;

(x) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 40;

(y) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 41;

(z) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 57;

(aa) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 58; or

(ab) both (t) and (u), both (t) and (w), both (u) and (v), both (v) and (w), both (x) and (y), both (x) and (aa), both (y) and (z), or both (z) and (aa).

28. An isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR according to any one of claims 1-13, the polypeptide according to any one of claims 14-20, or the protein according to any one of claims 21-27.

29. An isolated or purified nucleic acid comprising, from 5’ to 3’, a first nucleic acid sequence and a second nucleotide sequence, wherein the first and second nucleotide sequence, respectively, encode the amino sequences of SEQ ID NOs: 7 and 8; 51 and 8; 7 and 52; 51 and 52; 8 and 7; 8 and 51; 52 and 7; 52 and 51; 21 and 22; 53 and 22; 21 and 54; 53 and 54; 22 and 21; 22 and 53; 54 and 21; 54 and 53; 23 and 24; 55 and 24; 23 and 56; 55 and 56; 24 and 23; 24 and 55; 56 and 23; 56 and 55; 32 and 33; 33 and 32; 59 and 60; 60 and 59; 34 and 35; 35 and 34; 61 and 62; 62 and 61; 36 and 37; 37 and 36; 63 and 64; 64 and 63; 40 and 41; 57 and 41; 40 and 58; 57 and 58; 41 and 40; 41 and 57; 58 and 40; 58 and 57; 42 and 43; 43 and 42; 65 and 66; or 66 and 65.

30. The isolated or purified nucleic acid according to claim 29, further comprising a third nucleotide sequence interposed between the first and second nucleotide sequence, wherein the third nucleotide sequence encodes a cleavable linker peptide.

31. The isolated or purified nucleic acid according to claim 30, wherein the cleavable linker peptide comprises the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 25).

32. A recombinant expression vector comprising the nucleic acid according to any one of claims 28-31.

33. The recombinant expression vector according to claim 32, which is a transposon or a lentiviral vector.

34. An isolated or purified TCR, polypeptide, or protein encoded by the nucleic acid according to any one of claims 28-31 or the vector according to claim 32 or 33.

35. An isolated or purified TCR, polypeptide, or protein that results from expression of the nucleic acid according to any one of claims 28-31 or the vector according to claim 32 or 33 in a cell.

36. A method of producing a host cell expressing a TCR that has antigenic specificity for the peptide of VVVGADGVGK (SEQ ID NO: 29), the method comprising contacting a cell with the vector according to claim 32 or 33 under conditions that allow introduction of the vector into the cell.

37. An isolated or purified host cell comprising the nucleic acid according to any one of claims 28-31 or the recombinant expression vector according to claim 32 or 33.

38. The host cell according to claim 37, wherein the cell is a human lymphocyte.

39. The host cell according to claim 37 or 38, wherein the cell is selected from a T cell, a natural killer T (NKT) cell, an invariant natural killer T (iNKT) cell, and a natural killer (NK) cell.

40. An isolated or purified population of cells comprising the host cell according to any one of claims 37-39.

41. A method of producing the TCR according to any one of claims 1-13, 34, or 35, the polypeptide according to any one of claims 14-20, 34, or 35, or the protein according to any one of claims 21-27, 34, or 35, the method comprising culturing the host cell according to any one of claims 37-39, or the population of host cells according to claim 40, so that the TCR, polypeptide, or protein is produced.

42. A pharmaceutical composition comprising (a) the TCR according to any one of claims 1-13, 34, or 35, the polypeptide according to any one of claims 14-20, 34, or 35, the protein according to any one of claims 21-27, 34, or 35, the nucleic acid according to any one of claims 28-31, the recombinant expression vector according to claim 32 or 33, the host cell according to any one of claims 37-39, or the population of cells according to claim 40 and (b) a pharmaceutically acceptable carrier.

43. A method of detecting the presence of cancer in a mammal, the method comprising:

(a) contacting a sample comprising cells of the cancer with the TCR according to any one of claims 1-13, 34, or 35, the polypeptide according to any one of claims 14-20, 34, or 35, the protein according to any one of claims 21-27, 34, or 35, the nucleic acid according to any one of claims 28-31, the recombinant expression vector according to claim 32 or 33, the host cell according to any one of claims 37-39, the population of cells according to claim 40, or the pharmaceutical composition of claim 42, thereby forming a complex; and

(b) detecting the complex,

wherein detection of the complex is indicative of the presence of cancer in the mammal.

44. The TCR according to any one of claims 1-13, 34, or 35, the polypeptide according to any one of claims 14-20, 34, or 35, the protein according to any one of claims 21-27, 34, or 35, the nucleic acid according to any one of claims 28-31, the recombinant expression vector according to claim 32 or 33, the host cell according to any one of claims 37-39, the population of cells according to claim 40, or the pharmaceutical composition according to claim 42 for use in inducing an immune response against cancer in a mammal.

45. The TCR according to any one of claims 1-13, 34, or 35, the polypeptide according to any one of claims 14-20, 34, or 35, the protein according to any one of claims 21-27, 34, or 35, the nucleic acid according to any one of claims 28-31, the recombinant expression vector according to claim 32 or 33, the host cell according to any one of claims 37-39, the population of cells according to claim 40, or the pharmaceutical composition of claim 42 for use in treating or preventing cancer in a mammal.

46. The method according to claim 43 or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for use according to claim 44 or 45, wherein the cancer expresses a mutated human RAS amino acid sequence with a substitution of glycine at position 12 with aspartic acid,

wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS), a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS), or a mutated human Neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence, and

wherein position 12 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS protein, respectively.

47. The method or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for use according toclaim 46, wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS) amino acid sequence.

48. The method or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for use according toclaim 46, wherein the mutated human RAS amino acid sequence is a mutated human neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.

49. The method or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for use according toclaim 46, wherein the mutated human RAS amino acid sequence is a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS) amino acid sequence.

50. The method according to any one of claims 43 or 46-49 or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for use according to any one of claims 44-49, wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

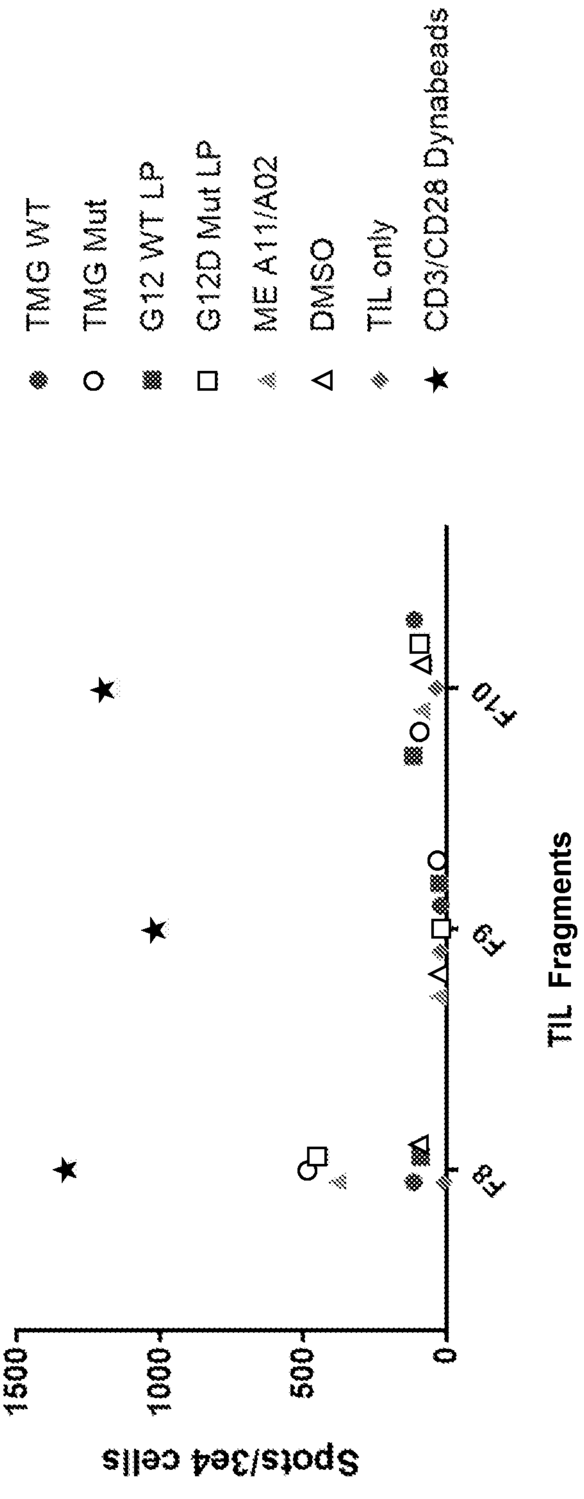
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Fig. 1A

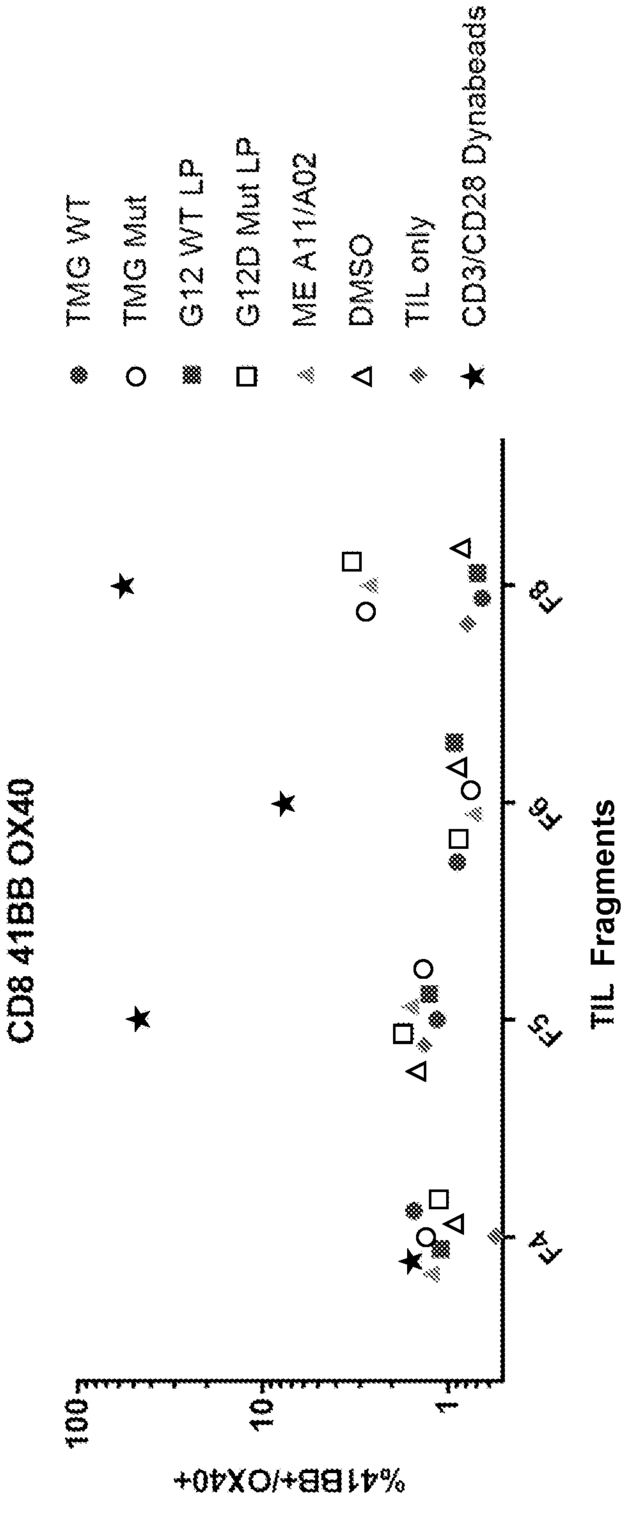
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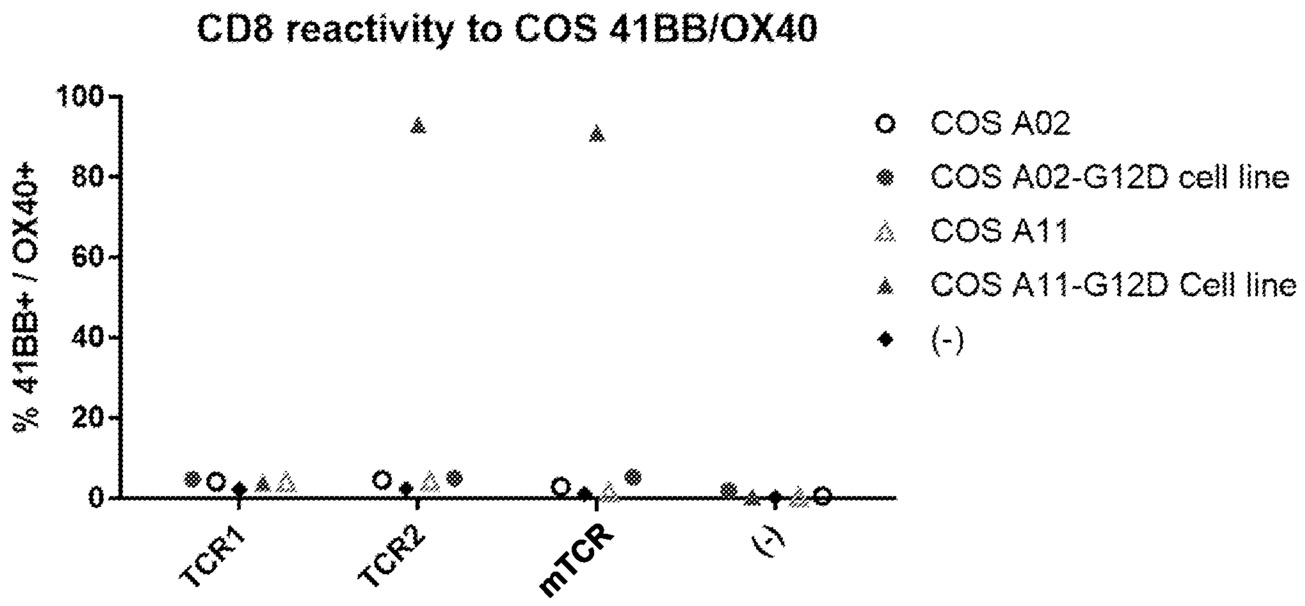
Fig. 1B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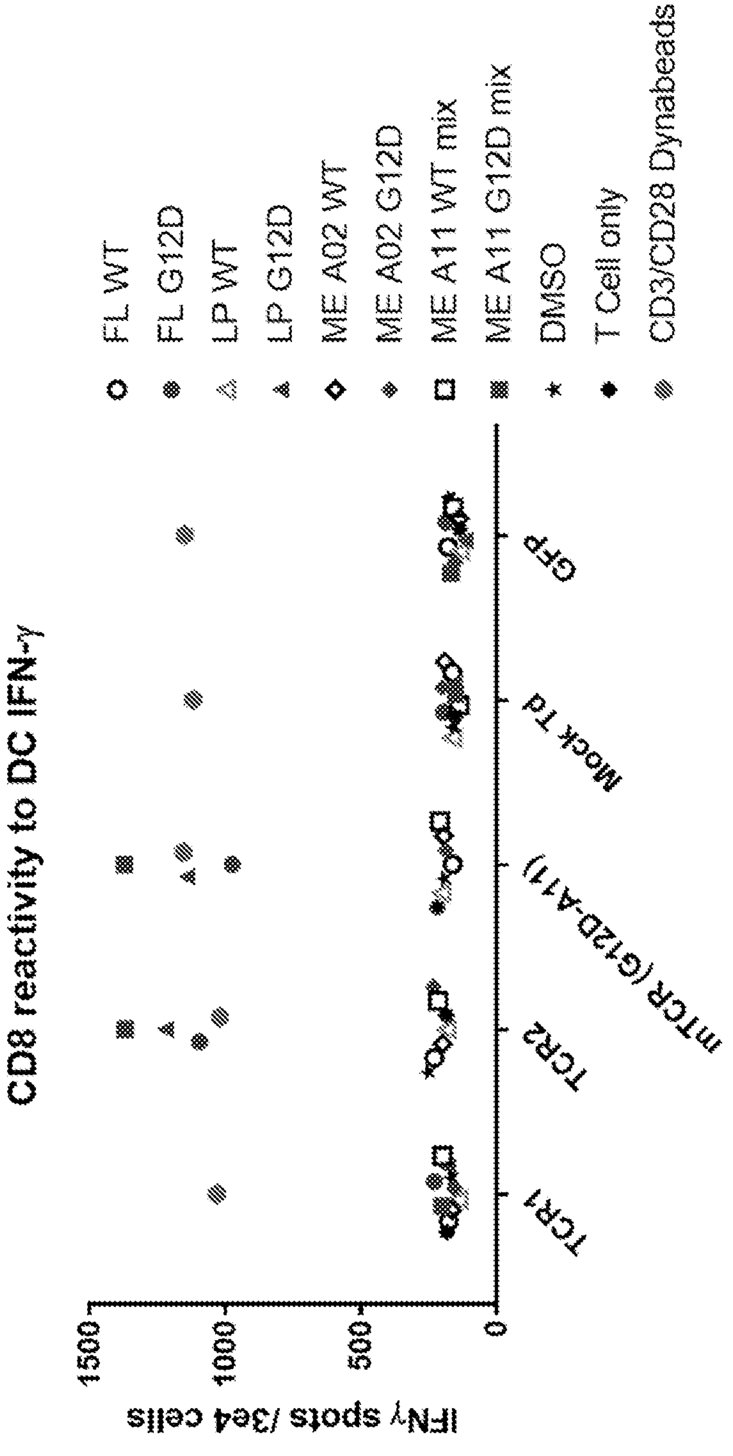
% 41BB+ / OX40+
100
80
60
40
20
0
TCR1
TCR2
mTCR
(-)
COS A02
COS A02-G12D cell line
COS A11
COS A11-G12D Cell line
(-)

Fig. 2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1000
500
0
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TCR2
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Mock Td
GFP
FL WT
FL G12D
LP WT
LP G12D
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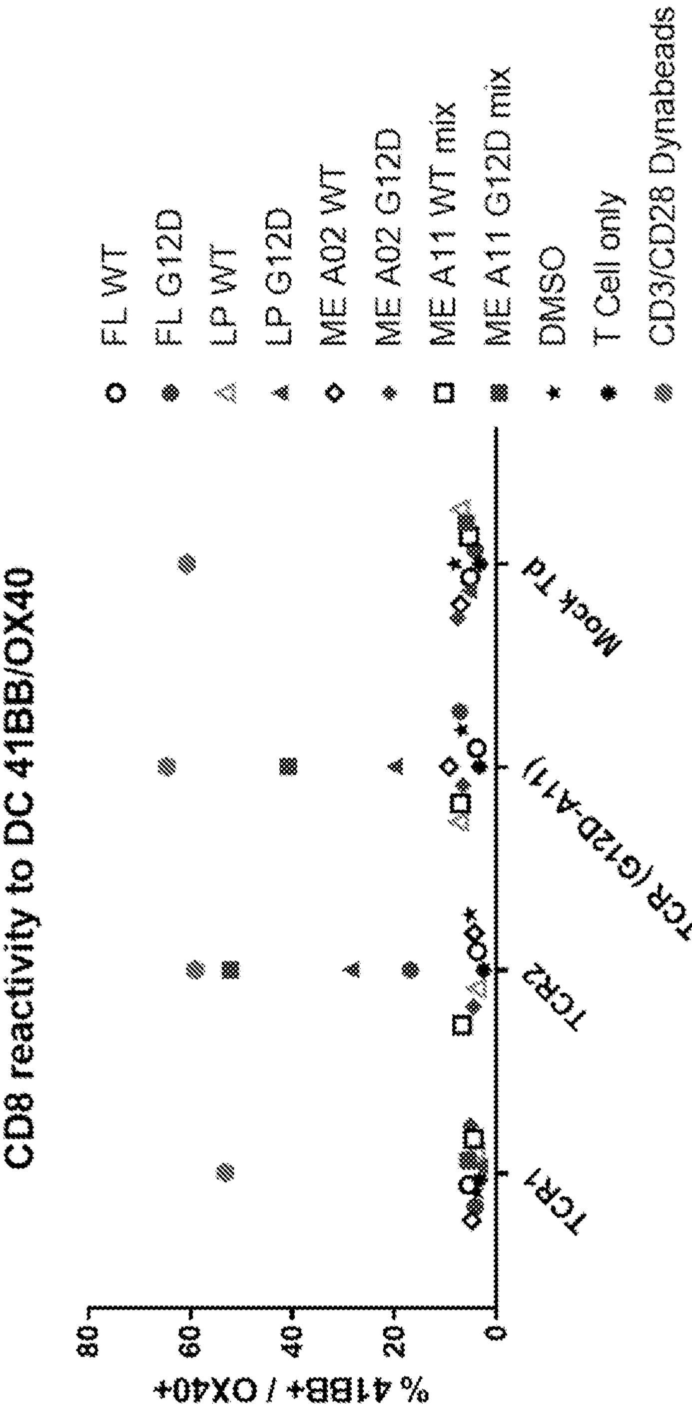
ME A02 G12D
ME A11 WT mix
ME A11 G12D mix
DMSO
T Cell only
CD3/CD28 Dynabeads

Fig. 3A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% 41BB+ / OX40+
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40
20
0
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TCR2
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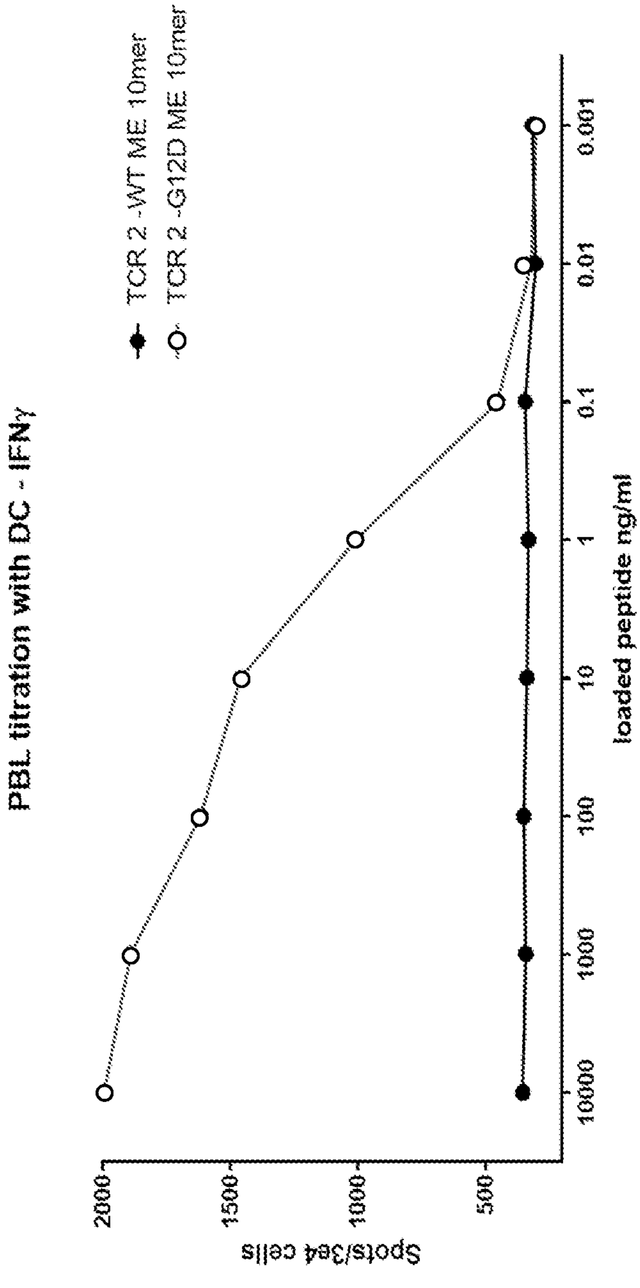
Mock Td
○ FL WT
● FL G12D
△ LP WT
▲ LP G12D
◇ ME A02 WT
◆ ME A02 G12D
□ ME A11 WT mix
■ ME A11 G12D mix
★ DMSO
● T Cell only
● CD3/CD28 Dynabeads

Fig. 3B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TCR 2 -G12D ME 10mer
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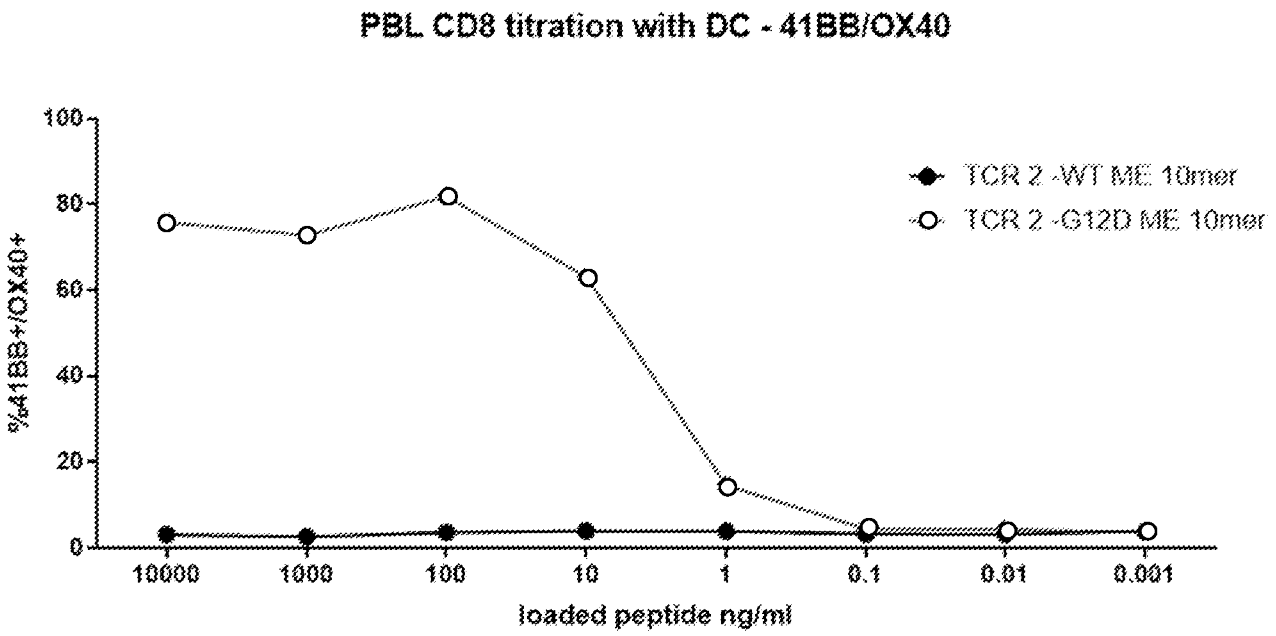
10
1
0.1
0.01
0.001
loaded peptide ng/ml

Fig. 4A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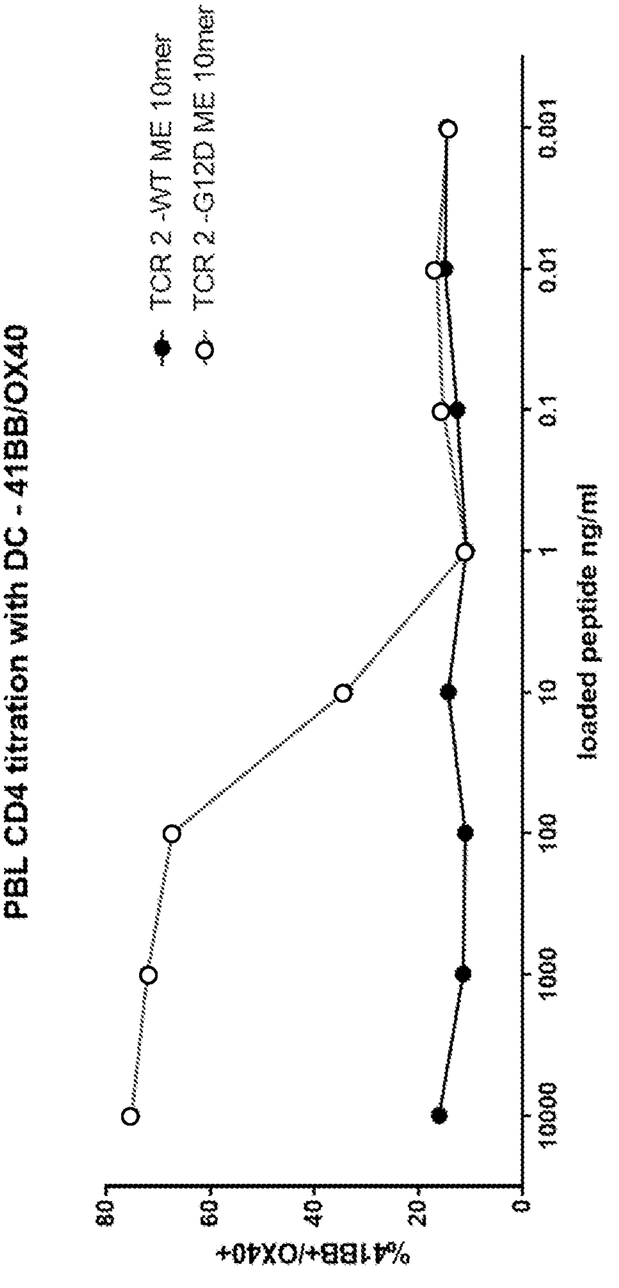
TCR 2 -G12D ME 10mer

Fig. 4B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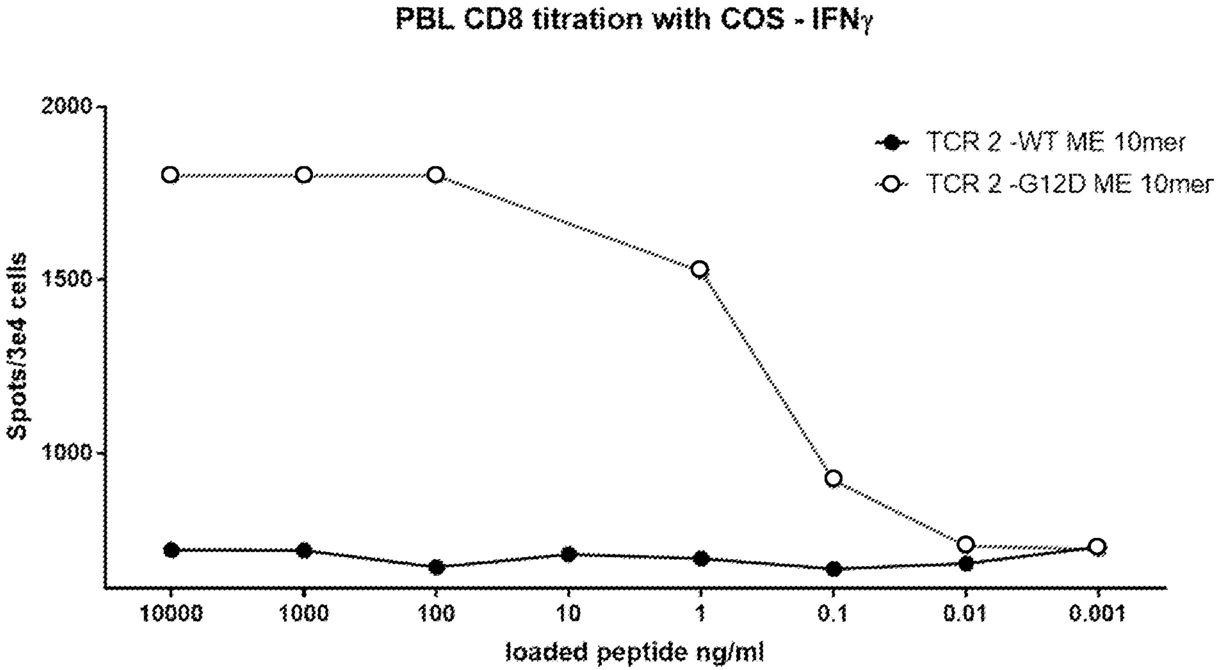
TCR 2 -G12D ME 10mer

Fig. 4C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Spots/3e4 cells
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10000
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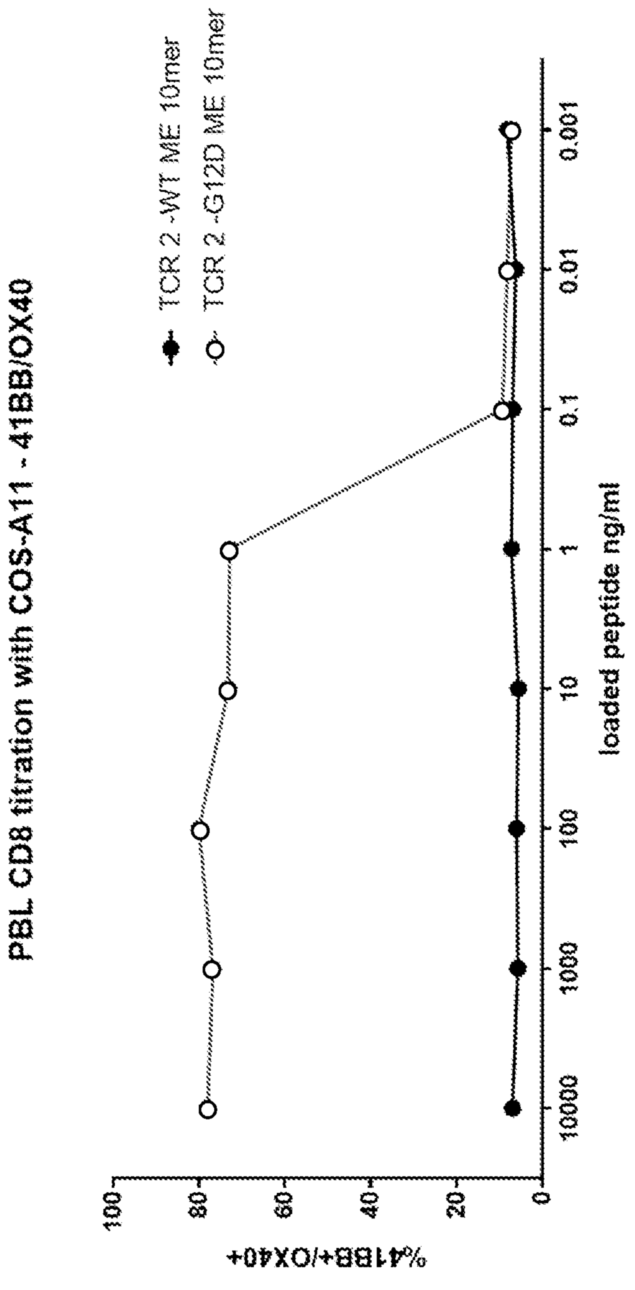
loaded peptide ng/ml

Fig. 5A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TCR 2 -G12D ME 10mer
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10
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0.01
0.001
loaded peptide ng/ml

Fig. 5B

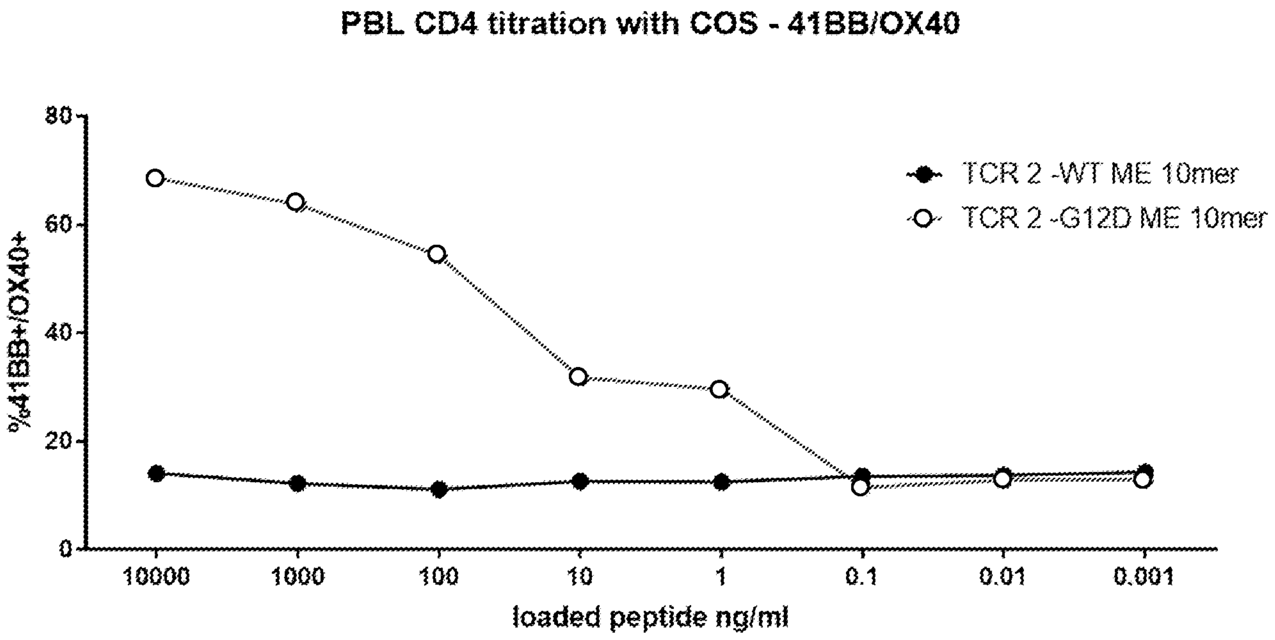
PBL CD4 titration with COS - 41BB/OX40

Fig. 5C

SEQUENCE LISTING

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       SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35                  40                  45


Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
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Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65                  70                  75                  80
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Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85   90   95

Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100   105   110

Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115   120   125

Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130   135   140

Pro
145

<210> 8
<211> 134
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 8

Met Ala Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1   5   10   15

Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20   25   30

Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35   40   45

Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50   55   60

Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65   70   75   80

Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85   90   95

```
Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110


Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125


Thr Arg Leu Thr Val Leu
    130


<210>  9
<211>  189
<212>  PRT
<213>  Homo sapiens

<400>  9

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30


Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45


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


Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80


Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
                85                  90                  95


Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
            100                 105                 110


Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
        115                 120                 125


Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
```

```
    130                 135                 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys
                165                 170                 175

Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Ile Met
            180                 185


<210>  10
<211>  188
<212>  PRT
<213>  Homo sapiens

<400>  10

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1               5                   10                  15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45

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

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80

Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
                85                  90                  95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
            100                 105                 110

Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
        115                 120                 125
```

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130   135   140

Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145   150   155   160

Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
                165   170   175

Lys Lys Lys Lys Ser Lys Thr Lys Cys Val Ile Met
            180   185

<210> 11
<211> 189
<212> PRT
<213> Homo sapiens

<400> 11

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1   5   10   15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20   25   30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35   40   45

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

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65   70   75   80

Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His Gln Tyr
                85   90   95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100   105   110

Leu Val Gly Asn Lys Cys Asp Leu Ala Ala Arg Thr Val Glu Ser Arg
        115   120   125

```
Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
    130                 135                 140


Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160


Arg Glu Ile Arg Gln His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
                165                 170                 175


Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
            180                 185


<210>  12
<211>  189
<212>  PRT
<213>  Homo sapiens

<400>  12

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30


Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45


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


Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80


Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
                85                  90                  95


Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100                 105                 110


Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
        115                 120                 125
```

```
Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140


Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160


Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
                165                 170                 175


Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
            180                 185


<210>  13
<211>  189
<212>  PRT
<213>  Homo sapiens

<400>  13

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Asp Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30


Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45


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


Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80


Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
                85                  90                  95


Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
            100                 105                 110


Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
```

```
        115                 120                 125

Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140

Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160

Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys
                165                 170                 175

Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Ile Met
            180                 185


<210>  14
<211>  188
<212>  PRT
<213>  Homo sapiens

<400>  14

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Asp Gly Val Gly Lys
1               5                   10                  15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45

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

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80

Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr
                85                  90                  95

Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val
            100                 105                 110
```

```
Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys
        115                 120                 125


Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130                 135                 140


Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160


Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys
                165                 170                 175


Lys Lys Lys Lys Ser Lys Thr Lys Cys Val Ile Met
            180                 185


<210>  15
<211>  189
<212>  PRT
<213>  Homo sapiens

<400>  15

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Asp Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30


Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45


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


Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80


Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His Gln Tyr
                85                  90                  95


Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100                 105                 110
```

```
Leu Val Gly Asn Lys Cys Asp Leu Ala Ala Arg Thr Val Glu Ser Arg
        115                 120                 125


Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr
    130                 135                 140


Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145                 150                 155                 160


Arg Glu Ile Arg Gln His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu
                165                 170                 175


Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser
            180                 185


<210>  16
<211>  189
<212>  PRT
<213>  Homo sapiens

<400>  16

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Asp Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr
            20                  25                  30


Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly
        35                  40                  45


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


Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys
65                  70                  75                  80


Val Phe Ala Ile Asn Asn Ser Lys Ser Phe Ala Asp Ile Asn Leu Tyr
                85                  90                  95


Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val
            100                 105                 110
```

Leu Val Gly Asn Lys Cys Asp Leu Pro Thr Arg Thr Val Asp Thr Lys
        115   120   125

Gln Ala His Glu Leu Ala Lys Ser Tyr Gly Ile Pro Phe Ile Glu Thr
    130   135   140

Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val
145   150   155   160

Arg Glu Ile Arg Gln Tyr Arg Met Lys Lys Leu Asn Ser Ser Asp Asp
                165   170   175

Gly Thr Gln Gly Cys Met Gly Leu Pro Cys Val Val Met
            180   185

<210> 17
<211> 137
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> MISC_FEATURE
<222> (48)..(48)
<223> Xaa is Thr or Cys

<220>
<221> MISC_FEATURE
<222> (112)..(112)
<223> Xaa is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<220>
<221> MISC_FEATURE
<222> (114)..(114)
<223> Xaa is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp

<220>
<221> MISC_FEATURE
<222> (115)..(115)
<223> Xaa is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<400> 17

Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg

```
1               5                   10                  15


Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile
            20                  25                  30


Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Xaa
        35                  40                  45


Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala
    50                  55                  60


Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr
65                  70                  75                  80


Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr
                85                  90                  95


Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Xaa
            100                 105                 110


Val Xaa Xaa Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu
        115                 120                 125


Leu Met Thr Leu Arg Leu Trp Ser Ser
    130                 135


<210>  18
<211>  173
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (57)..(57)
<223>  Xaa is Ser or Cys

<400>  18

Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu Pro
1               5                   10                  15
```

```
Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys Leu
            20                  25                  30


Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn
        35                  40                  45


Gly Lys Glu Val His Ser Gly Val Xaa Thr Asp Pro Gln Ala Tyr Lys
    50                  55                  60


Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
65                  70                  75                  80


Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe
                85                  90                  95


His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro
            100                 105                 110


Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
        115                 120                 125


Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu
    130                 135                 140


Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
145                 150                 155                 160


Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
                165                 170


<210>  19
<211>  137
<212>  PRT
<213>  Mus musculus

<400>  19

Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg
1               5                   10                  15


Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile
            20                  25                  30
```

```
Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Thr
        35                  40                  45


Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala
    50                  55                  60


Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr
65                  70                  75                  80


Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr
                85                  90                  95


Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Ser
            100                 105                 110


Val Met Gly Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu
        115                 120                 125


Leu Met Thr Leu Arg Leu Trp Ser Ser
    130                 135


<210>  20
<211>  173
<212>  PRT
<213>  Mus musculus

<400>  20

Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu Pro
1               5                   10                  15


Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys Leu
            20                  25                  30


Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn
        35                  40                  45


Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Ala Tyr Lys
    50                  55                  60


Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
```

```
65                  70                  75                  80

Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe
                85                  90                  95

His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro
            100                 105                 110

Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
        115                 120                 125

Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu
    130                 135                 140

Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
145                 150                 155                 160

Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
                165                 170


<210>  21
<211>  282
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (193)..(193)
<223>  Xaa is Thr or Cys

<220>
<221>  MISC_FEATURE
<222>  (257)..(257)
<223>  Xaa is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<220>
<221>  MISC_FEATURE
<222>  (259)..(259)
<223>  Xaa is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp

<220>
<221>  MISC_FEATURE
<222>  (260)..(260)
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<223>  Xaa is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<400>  21

Met Asp Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1               5                   10                  15


Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20                  25                  30


Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35                  40                  45


Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50                  55                  60


Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65                  70                  75                  80


Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85                  90                  95


Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100                 105                 110


Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115                 120                 125


Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130                 135                 140


Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160


Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175


Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190


Xaa Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
        195                 200                 205
```

```
Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220


Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240


Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255


Xaa Val Xaa Xaa Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270


Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
        275                 280


<210>  22
<211>  307
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (191)..(191)
<223>  Xaa is Ser or Cys

<400>  22

Met Ala Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30


Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45


Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60
```

```
Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80

Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95

Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110

Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140

Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160

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

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Xaa Thr
            180                 185                 190

Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205

Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220

Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240

Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255

Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285
```

Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290   295   300

Lys Asn Ser
305

<210> 23
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 23

Met Asp Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1   5   10   15

Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20   25   30

Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35   40   45

Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50   55   60

Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65   70   75   80

Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85   90   95

Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100   105   110

Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115   120   125

Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130   135   140

```
Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160


Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175


Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190


Thr Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
        195                 200                 205


Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220


Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240


Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255


Ser Val Met Gly Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270


Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
        275                 280


<210>  24
<211>  307
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  24

Met Ala Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30
```

```
Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45

Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60

Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80

Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95

Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110

Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140

Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160

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

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
            180                 185                 190

Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205

Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220

Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240
```

```
Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255


Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270


Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285


Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290                 295                 300


Lys Asn Ser
305


<210>  25
<211>  27
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  25

Arg Ala Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys
1               5                   10                  15


Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro
            20                  25


<210>  26
<211>  24
<212>  PRT
<213>  Homo sapiens

<400>  26

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Asp Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile
            20


<210>  27
```

<211> 24
<212> PRT
<213> Homo sapiens

<400> 27

```
Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1               5                   10                  15


Ser Ala Leu Thr Ile Gln Leu Ile
            20
```

<210> 28
<211> 9
<212> PRT
<213> Homo sapiens

<400> 28

```
Val Val Gly Ala Asp Gly Val Gly Lys
1               5
```

<210> 29
<211> 10
<212> PRT
<213> Homo sapiens

<400> 29

```
Val Val Val Gly Ala Asp Gly Val Gly Lys
1               5                   10
```

<210> 30
<211> 9
<212> PRT
<213> Homo sapiens

<400> 30

```
Val Val Gly Ala Gly Gly Val Gly Lys
1               5
```

<210> 31
<211> 10
<212> PRT
<213> Homo sapiens

<400> 31

Val Val Val Gly Ala Gly Gly Val Gly Lys
1   5   10

<210> 32
<211> 117
<212> PRT
<213> Homo sapiens

<400> 32

Gln Gln Gln Val Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly
1   5   10   15

Gly Ile Ser Ile Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr
            20   25   30

Phe Pro Trp Tyr Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile
        35   40   45

Ala Ile Arg Pro Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile
    50   55   60

Ser Phe Asn Lys Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser
65   70   75   80

Gln Pro Gly Asp Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn
                85   90   95

His Arg Gly Ser Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln
            100   105   110

Leu Thr Val Trp Pro
        115

<210> 33
<211> 115
<212> PRT
<213> Homo sapiens

<400> 33

Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly
1   5   10   15

```
Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val
            20                  25                  30


Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu
        35                  40                  45


Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe
    50                  55                  60


Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr
65                  70                  75                  80


Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala
                85                  90                  95


Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu
            100                 105                 110


Thr Val Leu
        115
```

<210> 34
<211> 254
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> MISC_FEATURE
<222> (165)..(165)
<223> Xaa is Thr or Cys

<220>
<221> MISC_FEATURE
<222> (229)..(229)
<223> Xaa is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<220>
<221> MISC_FEATURE
<222> (231)..(231)
<223> Xaa is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp

<220>
<221> MISC_FEATURE

```
<222>  (232)..(232)
<223>  Xaa is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<400>  34

Gln Gln Gln Val Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly
1               5                   10                  15


Gly Ile Ser Ile Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr
            20                  25                  30


Phe Pro Trp Tyr Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile
        35                  40                  45


Ala Ile Arg Pro Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile
    50                  55                  60


Ser Phe Asn Lys Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser
65                  70                  75                  80


Gln Pro Gly Asp Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn
                85                  90                  95


His Arg Gly Ser Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln
            100                 105                 110


Leu Thr Val Trp Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln
        115                 120                 125


Leu Lys Asp Pro Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp
    130                 135                 140


Phe Asp Ser Gln Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe
145                 150                 155                 160


Ile Thr Asp Lys Xaa Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser
                165                 170                 175


Asn Gly Ala Ile Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp
            180                 185                 190


Ile Phe Lys Glu Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys
```

```
        195                 200                 205

Asp Ala Thr Leu Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn
    210                 215                 220

Phe Gln Asn Leu Xaa Val Xaa Xaa Leu Arg Ile Leu Leu Leu Lys Val
225                 230                 235                 240

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
                245                 250


<210>  35
<211>  288
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (172)..(172)
<223>  Xaa is Ser or Cys

<400>  35

Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly
1               5                   10                  15

Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val
            20                  25                  30

Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu
        35                  40                  45

Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe
    50                  55                  60

Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr
65                  70                  75                  80

Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala
                85                  90                  95
```

```
Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu
            100                 105                 110


Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu
        115                 120                 125


Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu
    130                 135                 140


Val Cys Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
145                 150                 155                 160


Trp Val Asn Gly Lys Glu Val His Ser Gly Val Xaa Thr Asp Pro Gln
                165                 170                 175


Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg
            180                 185                 190


Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln
        195                 200                 205


Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser
    210                 215                 220


Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala
225                 230                 235                 240


Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala
                245                 250                 255


Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val
            260                 265                 270


Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
        275                 280                 285


<210>  36
<211>  254
<212>  PRT
<213>  Artificial Sequence
```

```
<220>
<223>  Synthetic

<400>  36

Gln Gln Gln Val Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly
1               5                   10                  15


Gly Ile Ser Ile Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr
            20                  25                  30


Phe Pro Trp Tyr Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile
        35                  40                  45


Ala Ile Arg Pro Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile
    50                  55                  60


Ser Phe Asn Lys Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser
65                  70                  75                  80


Gln Pro Gly Asp Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn
                85                  90                  95


His Arg Gly Ser Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln
            100                 105                 110


Leu Thr Val Trp Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln
        115                 120                 125


Leu Lys Asp Pro Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp
    130                 135                 140


Phe Asp Ser Gln Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe
145                 150                 155                 160


Ile Thr Asp Lys Thr Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser
                165                 170                 175


Asn Gly Ala Ile Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp
            180                 185                 190


Ile Phe Lys Glu Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys
```

```
        195                 200                 205

Asp Ala Thr Leu Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn
    210                 215                 220

Phe Gln Asn Leu Ser Val Met Gly Leu Arg Ile Leu Leu Leu Lys Val
225                 230                 235                 240

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
                245                 250


<210>  37
<211>  288
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  37

Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly
1               5                   10                  15

Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val
            20                  25                  30

Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu
        35                  40                  45

Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe
    50                  55                  60

Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr
65                  70                  75                  80

Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala
                85                  90                  95

Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu
            100                 105                 110

Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu
```

```
        115                 120                 125

Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu
    130                 135                 140

Val Cys Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
145                 150                 155                 160

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
                165                 170                 175

Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg
            180                 185                 190

Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln
        195                 200                 205

Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser
    210                 215                 220

Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala
225                 230                 235                 240

Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala
                245                 250                 255

Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val
            260                 265                 270

Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
        275                 280                 285


<210>  38
<211>  137
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  38

Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg
```

```
1               5                   10                  15


Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile
            20                  25                  30


Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Cys
        35                  40                  45


Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala
    50                  55                  60


Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr
65                  70                  75                  80


Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr
                85                  90                  95


Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Leu
            100                 105                 110


Val Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu
        115                 120                 125


Leu Met Thr Leu Arg Leu Trp Ser Ser
    130                 135


<210>  39
<211>  173
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  39

Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu Pro
1               5                   10                  15


Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys Leu
            20                  25                  30


Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn
```

```
        35                  40                  45

Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln Ala Tyr Lys
    50                  55                  60

Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
65                  70                  75                  80

Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe
                85                  90                  95

His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro
            100                 105                 110

Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
        115                 120                 125

Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu
    130                 135                 140

Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
145                 150                 155                 160

Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
                165                 170


<210>  40
<211>  282
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  40

Met Asp Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1               5                   10                  15

Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20                  25                  30

Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
```

```
        35                  40                  45

Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50                  55                  60

Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65                  70                  75                  80

Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85                  90                  95

Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100                 105                 110

Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115                 120                 125

Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130                 135                 140

Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160

Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175

Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190

Cys Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
        195                 200                 205

Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220

Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240

Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255
```

```
Leu Val Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270


Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
        275                 280


<210>  41
<211>  307
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  41

Met Ala Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30


Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45


Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60


Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80


Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95


Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110


Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125


Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140
```

```
Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160

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

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
            180                 185                 190

Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205

Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220

Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240

Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255

Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285

Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290                 295                 300

Lys Asn Ser
305


<210>  42
<211>  254
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  42
```

```
Gln Gln Gln Val Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly
1               5                   10                  15

Gly Ile Ser Ile Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr
            20                  25                  30

Phe Pro Trp Tyr Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile
        35                  40                  45

Ala Ile Arg Pro Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile
    50                  55                  60

Ser Phe Asn Lys Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser
65                  70                  75                  80

Gln Pro Gly Asp Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn
                85                  90                  95

His Arg Gly Ser Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln
            100                 105                 110

Leu Thr Val Trp Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln
        115                 120                 125

Leu Lys Asp Pro Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp
    130                 135                 140

Phe Asp Ser Gln Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe
145                 150                 155                 160

Ile Thr Asp Lys Cys Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser
                165                 170                 175

Asn Gly Ala Ile Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp
            180                 185                 190

Ile Phe Lys Glu Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys
        195                 200                 205

Asp Ala Thr Leu Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn
```

```
    210                 215                 220

Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu Leu Lys Val
225                 230                 235                 240

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
                245                 250


<210>  43
<211>  288
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  43

Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly
1               5                   10                  15

Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val
            20                  25                  30

Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu
        35                  40                  45

Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe
    50                  55                  60

Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr
65                  70                  75                  80

Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala
                85                  90                  95

Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu
            100                 105                 110

Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu
        115                 120                 125

Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu
```

```
    130                 135                 140

Val Cys Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
145                 150                 155                 160

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln
                165                 170                 175

Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg
            180                 185                 190

Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln
        195                 200                 205

Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser
    210                 215                 220

Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala
225                 230                 235                 240

Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala
                245                 250                 255

Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val
            260                 265                 270

Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
        275                 280                 285


<210>  44
<211>  435
<212>  DNA
<213>  Homo sapiens

<400>  44
atggacaaga tcctgggcgc ctcttttctg gtgctgtggc tgcagctgtg ctgggtgtcc        60

ggacagcaga aggagaagtc tgatcagcag caggtgaagc agtctcccca gagcctgatc       120

gtgcagaagg gcggcatcag catcatcaac tgtgcctacg agaataccgc cttcgattac       180

tttccctggt atcagcagtt cccaggcaag ggacccgccc tgctgatcgc aatcaggcct       240

gacgtgagcg agaagaagga gggccgcttc acaatcagct ttaataagtc cgccaagcag       300
```

ttctccctgc acatcatgga cagccagccc ggcgattccg ccacctactt ttgtgcagca   360

gaggcaggaa accacagggg ctccacactg ggccggctgt atttcggcag aggcacccag   420

ctgacagtgt ggcct   435

<210> 45
<211> 402
<212> DNA
<213> Homo sapiens

<400> 45
atggcctcca ggctgctgtg ctgggtgctg ctgtgcctgc tgggagcagg accagtgaag   60

gcaggcgtga cccagacacc taggtacctg atcaagaccc gcggccagca ggtgacactg   120

tcttgcagcc caatcagcgg ccaccgctcc gtgtcttggt accagcagac cccaggacag   180

ggcctgcagt tcctgtttga gtatttctcc gagacacaga ggaacaaggg caatttccct   240

ggccggtttt ctggcagaca gtttagcaac tcccgctctg agatgaacgt gagcaccctg   300

gagctgggcg atagcgccct gtacctgtgc gccagctccc tggccgcagg aggctatttc   360

aacgagcagt tctttggacc aggaaccagg ctgacagtgc tg   402

<210> 46
<211> 1859
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46
ccatggcctc caggctgctg tgctgggtgc tgctgtgcct gctgggagca ggaccagtga   60

aggcaggcgt gacccagaca cctaggtacc tgatcaagac ccgcggccag caggtgacac   120

tgtcttgcag cccaatcagc ggccaccgct ccgtgtcttg gtaccagcag accccaggac   180

agggcctgca gttcctgttt gagtatttct ccgagacaca gaggaacaag ggcaatttcc   240

ctggccggtt ttctggcaga cagtttagca actcccgctc tgagatgaac gtgagcaccc   300

tggagctggg cgatagcgcc ctgtacctgt gcgccagctc cctggccgca ggaggctatt   360

tcaacgagca gttctttgga ccaggaacca ggctgacagt gctggaggac ctgagaaatg   420

tgaccccccc taaggtgtcc ctgtttgagc cttctaaggc cgagatcgcc aacaagcaga   480 aggccaccct ggtgtgcctg gcaaggggct tctttccaga tcacgtggag ctgagctggt 540

gggtgaatgg caaggaggtg cactccggcg tgtgcaccga cccacaggcc tacaaggaga 600

gcaactactc ctattgtctg tctagccggc tgagagtgtc cgccacattc tggcacaacc 660

caaggaatca cttccgctgc caggtgcagt ttcacggcct gagcgaggag gataagtggc 720

cagagggctc cccaaagcca gtgacccaga atatctctgc cgaggcatgg ggaagggcag 780

actgtggaat caccagcgcc tcctatcagc agggcgtgct gagcgccaca atcctgtacg 840

agatcctgct gggcaaggcc accctgtatg ccgtgctggt gtccacactg gtggtcatgg 900

ctatggtgaa gagaaagaac tctagggcaa agcggagcgg aagcggagca accaatttca 960

gcctgctgaa gcaggcaggc gatgtggagg agaaccctgg accaatggac aagatcctgg 1020

gcgcctcttt tctggtgctg tggctgcagc tgtgctgggt gtccggacag cagaaggaga 1080

agtctgatca gcagcaggtg aagcagtctc cccagagcct gatcgtgcag aagggcggca 1140

tcagcatcat caactgtgcc tacgagaata ccgccttcga ttactttccc tggtatcagc 1200

agttcccagg caagggaccc gccctgctga tcgcaatcag gcctgacgtg agcgagaaga 1260

aggagggccg cttcacaatc agctttaata agtccgccaa gcagttctcc ctgcacatca 1320

tggacagcca gcccggcgat tccgccacct acttttgtgc agcagaggca ggaaaccaca 1380

ggggctccac actgggccgg ctgtatttcg gcagaggcac ccagctgaca gtgtggccta 1440

acatccagaa tcccgagcct gccgtgtacc agctgaagga cccaagatcc caggattcta 1500

ccctgtgcct gttcacagac tttgattctc agatcaatgt gcctaagaca atggagagcg 1560

gcacctttat cacagacaag tgcgtgctgg acatgaaggc tatggactcc aagtctaacg 1620

gcgccatcgc ctggtctaat cagaccagct tcacatgcca ggatatcttt aaggagacaa 1680

acgccacata tccttcctct gacgtgccat gtgatgccac cctgacagag aagagcttcg 1740

agacagacat gaacctgaat tttcagaacc tgctggtcat cgtgctgcgg atcctgctgc 1800

tgaaggtggc cggcttcaat ctgctgatga cactgagact gtggagctcc tgagaattc 1859

<210> 47
<211> 616
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

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<400>  47

Met Ala Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30


Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45


Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60


Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80


Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95


Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110


Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125


Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140


Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160


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


Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
            180                 185                 190


Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205
```

```
Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220

Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240

Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255

Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285

Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290                 295                 300

Lys Asn Ser Arg Ala Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser
305                 310                 315                 320

Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Asp
                325                 330                 335

Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu Cys Trp
            340                 345                 350

Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val Lys Gln
        355                 360                 365

Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn
    370                 375                 380

Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln
385                 390                 395                 400

Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro Asp Val
                405                 410                 415

Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala
```

```
            420                 425                 430

Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala
        435                 440                 445

Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser Thr Leu
    450                 455                 460

Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp Pro Asn
465                 470                 475                 480

Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg Ser
                485                 490                 495

Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile Asn
            500                 505                 510

Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Cys Val
        515                 520                 525

Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala Trp
    530                 535                 540

Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr Asn
545                 550                 555                 560

Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr Glu
                565                 570                 575

Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Leu Val
            580                 585                 590

Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu
        595                 600                 605

Met Thr Leu Arg Leu Trp Ser Ser
    610                 615

<210>  48
<211>  74
<212>  PRT
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<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys
1   5   10   15

Ser Ala Leu Thr Ile Gln Leu Ile Met Thr Glu Tyr Lys Leu Val Val
            20   25   30

Val Gly Ala Gly Gly Val Gly Lys Ser Ala Leu Thr Ile Gln Leu Ile
        35   40   45

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

Tyr Ser Ala Met Arg Asp Gln Tyr Met Arg
65   70

<210> 49
<211> 295
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Asp Gly Val Gly Lys
1   5   10   15

Ser Ala Leu Thr Ile Gln Leu Ile Met Thr Glu Tyr Lys Leu Val Val
            20   25   30

Val Gly Ala Val Gly Val Gly Lys Ser Ala Leu Thr Ile Gln Leu Ile
        35   40   45

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Cys Gly Val Gly Lys
    50   55   60

Ser Ala Leu Thr Ile Gln Leu Ile Met Thr Glu Tyr Lys Leu Val Val

```
65                  70                  75                  80

Val Gly Ala Ala Gly Val Gly Lys Ser Ala Leu Thr Ile Gln Leu Ile
                85                  90                  95

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Ser Gly Val Gly Lys
            100                 105                 110

Ser Ala Leu Thr Ile Gln Leu Ile Met Thr Glu Tyr Lys Leu Val Val
        115                 120                 125

Val Gly Ala Gly Asp Val Gly Lys Ser Ala Leu Thr Ile Gln Leu Ile
    130                 135                 140

Gln Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Arg Val Gly
145                 150                 155                 160

Lys Ser Ala Leu Thr Ile Gln Leu Ile Gln Met Thr Glu Tyr Lys Leu
                165                 170                 175

Val Val Val Gly Ala Gly Val Val Gly Lys Ser Ala Leu Thr Ile Gln
            180                 185                 190

Leu Ile Gln Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Arg
        195                 200                 205

Glu Glu Tyr Ser Ala Met Arg Asp Gln Tyr Met Arg Glu Thr Cys Leu
    210                 215                 220

Leu Asp Ile Leu Asp Thr Ala Gly Leu Glu Glu Tyr Ser Ala Met Arg
225                 230                 235                 240

Asp Gln Tyr Met Arg Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala
                245                 250                 255

Gly Lys Glu Glu Tyr Ser Ala Met Arg Asp Gln Tyr Met Arg Glu Thr
            260                 265                 270

Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly His Glu Glu Tyr Ser Ala
        275                 280                 285
```

Met Arg Asp Gln Tyr Met Arg
    290   295

<210> 50
<211> 10
<212> PRT
<213> Homo sapiens

<400> 50

Lys Leu Val Val Val Gly Ala Asp Gly Val
1   5   10

<210> 51
<211> 145
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 51

Met Ala Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1   5   10   15

Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20   25   30

Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35   40   45

Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50   55   60

Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65   70   75   80

Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85   90   95

Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100   105   110

Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115   120   125

Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130   135   140

Pro
145

<210> 52
<211> 134
<212> PRT
<213> Homo sapiens

<400> 52

Met Gly Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1   5   10   15

Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20   25   30

Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35   40   45

Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50   55   60

Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65   70   75   80

Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85   90   95

Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100   105   110

Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115   120   125

Thr Arg Leu Thr Val Leu
    130

<210> 53
<211> 282
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> MISC_FEATURE
<222> (193)..(193)
<223> Xaa is Thr or Cys

<220>
<221> MISC_FEATURE
<222> (257)..(257)
<223> Xaa is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<220>
<221> MISC_FEATURE
<222> (259)..(259)
<223> Xaa is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp

<220>
<221> MISC_FEATURE
<222> (260)..(260)
<223> Xaa is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<400> 53

Met Ala Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1   5   10   15

Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20   25   30

Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35   40   45

Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50   55   60

Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65   70   75   80

Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85   90   95

```
Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100                 105                 110

Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115                 120                 125

Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130                 135                 140

Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160

Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175

Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190

Xaa Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
        195                 200                 205

Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220

Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240

Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255

Xaa Val Xaa Xaa Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
        275                 280


<210>  54
<211>  307
<212>  PRT
<213>  Artificial Sequence
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<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (191)..(191)
<223>  Xaa is Ser or Cys

<400>  54

Met Gly Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30


Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45


Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60


Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80


Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95


Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110


Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125


Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140


Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160


Ala Thr Leu Val Cys Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu
                165                 170                 175
```

```
Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Xaa Thr
            180                 185                 190


Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205


Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220


Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240


Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255


Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270


Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285


Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290                 295                 300


Lys Asn Ser
305


<210>  55
<211>  282
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  55

Met Ala Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1               5                   10                  15


Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20                  25                  30
```

```
Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35                  40                  45

Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50                  55                  60

Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65                  70                  75                  80

Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85                  90                  95

Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100                 105                 110

Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115                 120                 125

Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130                 135                 140

Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160

Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175

Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190

Thr Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
        195                 200                 205

Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220

Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240
```

```
Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255


Ser Val Met Gly Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270


Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
        275                 280


<210>  56
<211>  307
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  56

Met Gly Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30


Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45


Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60


Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80


Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95


Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110


Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125
```

```
Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140

Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160

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

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
            180                 185                 190

Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205

Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220

Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240

Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255

Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285

Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290                 295                 300

Lys Asn Ser
305


<210>  57
<211>  282
<212>  PRT
<213>  Artificial Sequence

<220>
```

```
<223>  Synthetic

<400>  57

Met Ala Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1               5                   10                  15


Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20                  25                  30


Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35                  40                  45


Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50                  55                  60


Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65                  70                  75                  80


Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85                  90                  95


Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100                 105                 110


Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115                 120                 125


Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130                 135                 140


Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160


Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175


Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190


Cys Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
        195                 200                 205
```

```
Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220


Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240


Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255


Leu Val Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270


Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
        275                 280


<210>  58
<211>  307
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  58

Met Gly Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1               5                   10                  15


Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys
            20                  25                  30


Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His
        35                  40                  45


Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe
    50                  55                  60


Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro
65                  70                  75                  80


Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn
                85                  90                  95
```

```
Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser
            100                 105                 110

Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys
    130                 135                 140

Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys
145                 150                 155                 160

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

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr
            180                 185                 190

Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser
        195                 200                 205

Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe
    210                 215                 220

Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro
225                 230                 235                 240

Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp
                245                 250                 255

Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val
            260                 265                 270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
        275                 280                 285

Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg
    290                 295                 300
```

Lys Asn Ser
305

<210> 59
<211> 124
<212> PRT
<213> Homo sapiens

<400> 59

Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val Lys Gln Ser Pro Gln
1   5   10   15

Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20   25   30

Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35   40   45

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

Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
65   70   75   80

Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                85   90   95

Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser Thr Leu Gly Arg Leu
            100   105   110

Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp Pro
        115   120

<210> 60
<211> 113
<212> PRT
<213> Homo sapiens

<400> 60

Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly Gln Gln
1   5   10   15

```
Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val Ser Trp
            20                  25                  30


Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu Tyr Phe
        35                  40                  45


Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe Ser Gly
    50                  55                  60


Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr Leu Glu
65                  70                  75                  80


Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala Ala Gly
                85                  90                  95


Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu Thr Val
            100                 105                 110


Leu



<210>  61
<211>  261
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (172)..(172)
<223>  Xaa is Thr or Cys

<220>
<221>  MISC_FEATURE
<222>  (236)..(236)
<223>  Xaa is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<220>
<221>  MISC_FEATURE
<222>  (238)..(238)
<223>  Xaa is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp

<220>
<221>  MISC_FEATURE
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<222>  (239)..(239)
<223>  Xaa is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp

<400>  61

Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val Lys Gln Ser Pro Gln
1               5                   10                  15


Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20                  25                  30


Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35                  40                  45


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


Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
65                  70                  75                  80


Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                85                  90                  95


Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser Thr Leu Gly Arg Leu
            100                 105                 110


Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp Pro Asn Ile Gln Asn
        115                 120                 125


Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg Ser Gln Asp Ser
    130                 135                 140


Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile Asn Val Pro Lys
145                 150                 155                 160


Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Xaa Val Leu Asp Met
                165                 170                 175


Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala Trp Ser Asn Gln
            180                 185                 190


Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr Asn Ala Thr Tyr
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        195                 200                 205

Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr Glu Lys Ser Phe
    210                 215                 220

Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Xaa Val Xaa Xaa Leu
225                 230                 235                 240

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
                245                 250                 255

Arg Leu Trp Ser Ser
            260


<210>  62
<211>  286
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic


<220>
<221>  MISC_FEATURE
<222>  (170)..(170)
<223>  Xaa is Ser or Cys

<400>  62

Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly Gln Gln
1               5                   10                  15

Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val Ser Trp
            20                  25                  30

Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu Tyr Phe
        35                  40                  45

Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe Ser Gly
    50                  55                  60

Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr Leu Glu
65                  70                  75                  80
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Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala Ala Gly
                85   90   95

Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu Thr Val
            100   105   110

Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu
        115   120   125

Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys
    130   135   140

Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val
145   150   155   160

Asn Gly Lys Glu Val His Ser Gly Val Xaa Thr Asp Pro Gln Ala Tyr
                165   170   175

Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser
            180   185   190

Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln
        195   200   205

Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys
    210   215   220

Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys
225   230   235   240

Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile
                245   250   255

Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val
            260   265   270

Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
        275   280   285

<210> 63

<211> 261
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63

Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val Lys Gln Ser Pro Gln
1   5   10   15

Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20   25   30

Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35   40   45

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

Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
65   70   75   80

Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                85   90   95

Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser Thr Leu Gly Arg Leu
            100   105   110

Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp Pro Asn Ile Gln Asn
        115   120   125

Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg Ser Gln Asp Ser
    130   135   140

Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile Asn Val Pro Lys
145   150   155   160

Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Thr Val Leu Asp Met
                165   170   175

Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala Trp Ser Asn Gln

```
            180                 185                 190


Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr Asn Ala Thr Tyr
        195                 200                 205


Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr Glu Lys Ser Phe
    210                 215                 220


Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Ser Val Met Gly Leu
225                 230                 235                 240


Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
                245                 250                 255


Arg Leu Trp Ser Ser
            260


<210>  64
<211>  286
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  64

Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly Gln Gln
1               5                   10                  15


Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val Ser Trp
            20                  25                  30


Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu Tyr Phe
        35                  40                  45


Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe Ser Gly
    50                  55                  60


Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr Leu Glu
65                  70                  75                  80


Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala Ala Gly
```

```
                85                  90                  95

Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu Thr Val
            100                 105                 110

Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu
        115                 120                 125

Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys
    130                 135                 140

Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val
145                 150                 155                 160

Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Ala Tyr
                165                 170                 175

Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser
            180                 185                 190

Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln
        195                 200                 205

Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys
    210                 215                 220

Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys
225                 230                 235                 240

Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile
                245                 250                 255

Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val
            260                 265                 270

Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
        275                 280                 285

<210>  65
<211>  261
<212>  PRT
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<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  65

Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val Lys Gln Ser Pro Gln
1               5                   10                  15


Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile Ile Asn Cys Ala Tyr
            20                  25                  30


Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr Gln Gln Phe Pro Gly
        35                  40                  45


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


Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys Ser Ala Lys Gln Phe
65                  70                  75                  80


Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp Ser Ala Thr Tyr Phe
                85                  90                  95


Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser Thr Leu Gly Arg Leu
            100                 105                 110


Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp Pro Asn Ile Gln Asn
        115                 120                 125


Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg Ser Gln Asp Ser
    130                 135                 140


Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile Asn Val Pro Lys
145                 150                 155                 160


Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Cys Val Leu Asp Met
                165                 170                 175


Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala Trp Ser Asn Gln
            180                 185                 190
```

```
Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr Asn Ala Thr Tyr
        195                 200                 205


Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr Glu Lys Ser Phe
    210                 215                 220


Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu
225                 230                 235                 240


Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
                245                 250                 255


Arg Leu Trp Ser Ser
            260


<210>  66
<211>  286
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic

<400>  66

Gly Val Thr Gln Thr Pro Arg Tyr Leu Ile Lys Thr Arg Gly Gln Gln
1               5                   10                  15


Val Thr Leu Ser Cys Ser Pro Ile Ser Gly His Arg Ser Val Ser Trp
            20                  25                  30


Tyr Gln Gln Thr Pro Gly Gln Gly Leu Gln Phe Leu Phe Glu Tyr Phe
        35                  40                  45


Ser Glu Thr Gln Arg Asn Lys Gly Asn Phe Pro Gly Arg Phe Ser Gly
    50                  55                  60


Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn Val Ser Thr Leu Glu
65                  70                  75                  80


Leu Gly Asp Ser Ala Leu Tyr Leu Cys Ala Ser Ser Leu Ala Ala Gly
                85                  90                  95
```

```
Gly Tyr Phe Asn Glu Gln Phe Phe Gly Pro Gly Thr Arg Leu Thr Val
            100                 105                 110


Leu Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe Glu
        115                 120                 125


Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val Cys
    130                 135                 140


Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val
145                 150                 155                 160


Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln Ala Tyr
                165                 170                 175


Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser
            180                 185                 190


Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln
        195                 200                 205


Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys
    210                 215                 220


Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys
225                 230                 235                 240


Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile
                245                 250                 255


Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val
            260                 265                 270


Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
        275                 280                 285


<210>  67
<211>  616
<212>  PRT
<213>  Artificial Sequence
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```
<220>
<223>  Synthetic

<400>  67

Met Ala Lys Ile Leu Gly Ala Ser Phe Leu Val Leu Trp Leu Gln Leu
1               5                   10                  15


Cys Trp Val Ser Gly Gln Gln Lys Glu Lys Ser Asp Gln Gln Gln Val
            20                  25                  30


Lys Gln Ser Pro Gln Ser Leu Ile Val Gln Lys Gly Gly Ile Ser Ile
        35                  40                  45


Ile Asn Cys Ala Tyr Glu Asn Thr Ala Phe Asp Tyr Phe Pro Trp Tyr
    50                  55                  60


Gln Gln Phe Pro Gly Lys Gly Pro Ala Leu Leu Ile Ala Ile Arg Pro
65                  70                  75                  80


Asp Val Ser Glu Lys Lys Glu Gly Arg Phe Thr Ile Ser Phe Asn Lys
                85                  90                  95


Ser Ala Lys Gln Phe Ser Leu His Ile Met Asp Ser Gln Pro Gly Asp
            100                 105                 110


Ser Ala Thr Tyr Phe Cys Ala Ala Glu Ala Gly Asn His Arg Gly Ser
        115                 120                 125


Thr Leu Gly Arg Leu Tyr Phe Gly Arg Gly Thr Gln Leu Thr Val Trp
    130                 135                 140


Pro Asn Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
145                 150                 155                 160


Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
                165                 170                 175


Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
            180                 185                 190


Cys Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
```

```
        195                 200                 205

Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
    210                 215                 220

Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
225                 230                 235                 240

Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
                245                 250                 255

Leu Val Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
            260                 265                 270

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser Arg Ala Lys Arg Ser Gly
        275                 280                 285

Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu
    290                 295                 300

Glu Asn Pro Gly Pro Met Gly Ser Arg Leu Leu Cys Trp Val Leu Leu
305                 310                 315                 320

Cys Leu Leu Gly Ala Gly Pro Val Lys Ala Gly Val Thr Gln Thr Pro
                325                 330                 335

Arg Tyr Leu Ile Lys Thr Arg Gly Gln Gln Val Thr Leu Ser Cys Ser
            340                 345                 350

Pro Ile Ser Gly His Arg Ser Val Ser Trp Tyr Gln Gln Thr Pro Gly
        355                 360                 365

Gln Gly Leu Gln Phe Leu Phe Glu Tyr Phe Ser Glu Thr Gln Arg Asn
    370                 375                 380

Lys Gly Asn Phe Pro Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser
385                 390                 395                 400

Arg Ser Glu Met Asn Val Ser Thr Leu Glu Leu Gly Asp Ser Ala Leu
                405                 410                 415
```

```
Tyr Leu Cys Ala Ser Ser Leu Ala Ala Gly Gly Tyr Phe Asn Glu Gln
            420                 425                 430

Phe Phe Gly Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Arg Asn
        435                 440                 445

Val Thr Pro Pro Lys Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile
    450                 455                 460

Ala Asn Lys Gln Lys Ala Thr Leu Val Cys Leu Ala Arg Gly Phe Phe
465                 470                 475                 480

Pro Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His
                485                 490                 495

Ser Gly Val Cys Thr Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser
            500                 505                 510

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn
        515                 520                 525

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu
    530                 535                 540

Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile
545                 550                 555                 560

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser
                565                 570                 575

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
            580                 585                 590

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Thr Leu Val Val Met
        595                 600                 605

Ala Met Val Lys Arg Lys Asn Ser
    610                 615
```