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(54) Title: HLA CLASS II-RESTRICTED DQ T CELL RECEPTORS AGAINST RAS WITH G13D MUTATION

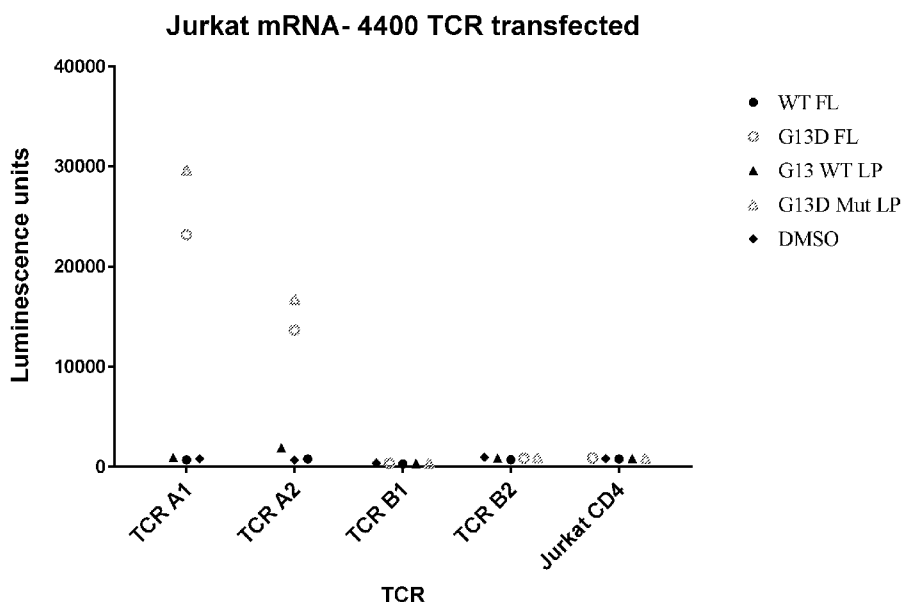


Fig. 5

(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 13 with aspartic acid. The TCRs may recognize G13D RAS presented by an HLA-DQ heterodimer. 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.



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HLA CLASS II-RESTRICTED DQ T CELL RECEPTORS AGAINST RAS WITH G13D MUTATION

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 63/086,674, filed October 2, 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 411,856 Byte ASCII (Text) file named “757694_ST25.txt,” dated September 23, 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) having antigenic specificity for a mutated human RAS amino acid sequence with a

substitution of glycine at position 13 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 13 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, (c) all of SEQ ID NOs: 1-6, (d) all of SEQ ID NOs: 11-13, (e) all of SEQ ID NOs: 14-16, (f) all of SEQ ID NOs: 11-16, (g) all of SEQ ID NOs: 21-23, (h) all of SEQ ID NOs: 24-26, (i) all of SEQ ID NOs: 21-26, (j) all of SEQ ID NOs: 31-33, (k) all of SEQ ID NOs: 34-36, (l) all of SEQ ID NOs: 31-36, (m) all of SEQ ID NOs: 41-43, (n) all of SEQ ID NOs: 44-46, (o) all of SEQ ID NOs: 41-46, (p) all of SEQ ID NOs: 119-121, (q) all of SEQ ID NOs: 122-124, (r) all of SEQ ID NOs: 119-124, (s) all of SEQ ID NOs: 129-131, (t) all of SEQ ID NOs: 132-134, (u) all of SEQ ID NOs: 129-134, (v) all of SEQ ID NOs: 139-141, (w) all of SEQ ID NOs: 142-144, (x) all of SEQ ID NOs: 139-144, (y) all of SEQ ID NOs: 149-151, (z) all of SEQ ID NOs: 152-154, (aa) all of SEQ ID NOs: 149-154, (bb) all of SEQ ID NOs: 159-161, (cc) all of SEQ ID NOs: 162-164, (dd) all of SEQ ID NOs: 159-164, (ee) all of SEQ ID NOs: 169-171, (ff) all of SEQ ID NOs: 172-174, (gg) all of SEQ ID NOs: 169-174, (hh) all of SEQ ID NOs: 179-181, (ii) all of SEQ ID NOs: 182-184, or (jj) all of SEQ ID NOs: 179-184.

[0007] Still another embodiment of the invention provides an isolated or purified protein, comprising: (a) 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; (b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 11-13 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 14-16; (c) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 21-23 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 24-26; (d) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 31-33 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 34-36; or (e) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 41-43 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 44-46;

(f) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 119-121 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 122-124; (g) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 129-131 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 132-134; (h) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 139-141 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 142-144; (i) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 149-151 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 152-154; (j) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 159-161 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 162-164; (k) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 169-171 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 172-174; or (l) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 179-181 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 182-184.

[0008] Further embodiments of the invention provide related 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; 8 and 7; 9 and 10; 10 and 9; 17 and 18; 18 and 17; 19 and 20; 20 and 19; 27 and 28; 28 and 27; 29 and 30; 30 and 29; 37 and 38; 38 and 37; 39 and 40; 40 and 39; 47 and 48; 48 and 47; 49 and 50; 50 and 49; 125 and 126; 126 and 125; 127 and 128; 128 and 127; 135 and 136; 136 and 135; 137 and 138; 138 and 137; 145 and 146; 146 and 145; 147 and 148; 148 and 147; 155 and 156; 156 and 155; 157 and 158; 158 and 157; 165 and 166; 166 and 165; 167 and 168; 168 and 167; 175 and 176; 176 and 175; 177 and 178; 178 and 177; 185 and 186; 186 and 185; 187 and 188; 188 and 187; 65 and 66; 66 and 65; 67 and 68; 68 and 67; 69 and 70; 70 and 69; 71 and 72; 72 and 71; 73 and 74; 74 and 73; 75 and 76; 76 and 75; 77 and 78; 78 and 77; 79 and 80; 80 and 79; 81 and 82; 82 and 81; 83 and 84; 84 and 83; 85 and 86; 86 and 85; 87 and 88; 88 and 87; 89 and 90; 90 and 89; 91 and 92; 92 and 91; 93 and 94; 94 and 93; 95 and 96; 96 and 95; 97 and 98; 98 and 97; 99 and 100; 100 and

99; 101 and 102; 102 and 101; 103 and 104; 104 and 103; 189 and 190; 190 and 189; 191 and 192; 192 and 191; 193 and 194; 194 and 193; 195 and 196; 196 and 195; 197 and 198; 198 and 197; 199 and 200; 200 and 199; 201 and 202; 202 and 201; 203 and 204; 204 and 203; 205 and 206; 206 and 205; 207 and 208; 208 and 207; 209 and 210; 210 and 209; 211 and 212; 212 and 211; 213 and 214; 214 and 213; 215 and 216; 216 and 215; 217 and 218; 218 and 217; 219 and 220; 220 and 219; 221 and 222; 222 and 221; 223 and 224; 224 and 223; 225 and 226; 226 and 225; 227 and 228; 228 and 227; 229 and 230; 230 and 229; 231 and 232; 232 and 231; 233 and 234; 234 and 233; 235 and 236; 236 and 235; 237 and 238; 238 and 237; 239 and 240; 240 and 239; 241 and 242; 242 and 241; 243 and 244; or 244 and 243.

[0010] Another embodiment of the invention provides a method of producing a host cell expressing a TCR that has antigenic specificity for the peptide of MTEYKLVVVGAGDVGKSALTIQLIQ (SEQ ID NO: 252), the method comprising contacting a cell with the inventive recombinant expression vector under conditions that allow introduction of the vector into the cell.

[0011] Still another embodiment of the invention provides a method of producing the inventive TCR, polypeptide, or protein, the method comprising culturing the inventive host cell or the population of host cells so that the inventive TCR, polypeptide, or protein is produced.

[0012] Another embodiment of the invention provides a method of detecting the presence of cancer in mammal, the method comprising: (a) contacting a sample comprising cells of the cancer with the inventive TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population, or pharmaceutical composition, thereby forming a complex; and (b) detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the mammal.

[0013] Another embodiment of the invention provides a method of inducing an immune response against cancer in a mammal, the method comprising administering to the mammal the inventive TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population, or pharmaceutical composition, in an amount effective to induce the immune response against cancer in the mammal.

[0014] Another embodiment of the invention provides a method of treating or preventing cancer in a mammal, the method comprising administering to the mammal the inventive TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population,

or pharmaceutical composition in an amount effective to treat or prevent cancer in the mammal.

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

[0015] Figure 1 is a graph showing IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay following co-culture of effector cells with target cells. Effector cells were TIL from tumor fragments (numbered F1-F8, F10-F16, and F18-F22) from patient 4400. Target cells were dendritic cells (DC) (i) transfected with mRNA encoding full length (FL) G13D KRAS or the corresponding FL wild-type (WT) KRAS; (ii) pulsed with the G13D 25-mer peptide (G13D LP) or the corresponding WT 25-mer peptide (WT LP); or (iii) pulsed with G13D ME “mix” (containing a combination of three predicted minimal epitopes from the mutated peptide). Effector cells (i) co-cultured with DC treated with DMSO or (ii) cultured alone (T cell only) served as negative controls. Effector cells treated with anti-CD3/CD28 antibodies served as a positive control.

[0016] Figures 2A-2B are graphs showing the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺ cells (Fig. 2A) or CD8⁺ cells (Fig. 2B) following co-culture of effector cells with target cells. Effector cells, target cells, and controls are as described for Figure 1.

[0017] Figure 3 is a graph showing IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay following co-culture of effector cells with target cells. Effector cells were (i) TIL from tumor fragments F15 and F16 that were untreated or treated as follows: (a) F16 TIL were stimulated *in vitro* (IVS) with DC pulsed with G13D 25-mer peptide or (b) F15 and F16 TIL were combined, activated (as described for Figs. 1 and 2A-2B), sorted for CD4⁺/41BB⁺/OX40⁺ expression, and underwent REP; or (ii) TIL from tumor fragments F21 and F22 that were combined, sorted for CD4⁺/41BB⁺/OX40⁺ or CD8⁺/41BB⁺/OX40⁺ expression, and underwent REP. Target cells and controls are as described for Figure 1. Reactive cells were single-cell sorted by FACS into a 96-well plate and were sequenced to provide the TCR alpha and TCR beta chains.

[0018] Figures 4A-4B are graphs showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay following co-culture of effector cells with target cells. Target cells were DC pulsed with the indicated concentrations (ng/mL) of G13D 25-mer peptide or the corresponding WT 25-mer peptide. Effector cells were the reactive cells from Fig. 3: TIL

from tumor fragment F16 following G13D IVS (Fig. 4A) or TIL from tumor fragments F15 and F16 following activation, sort for CD4⁺/41BB⁺/OX40⁺ and REP (Fig. 4B).

[0019] Figure 5 is a graph showing luciferase expression measured by luminescence units upon co-culture of effector cells with target cells. Effector cells were a Jurkat cell line stably expressing luciferase under the transcriptional control of an NFAT promotor and also stably expressing the CD4 co-receptor; these cells were virally transduced with mRNA encoding TCR alpha and beta chains generated according to the sequencing described for Fig. 3. The TCR was the 4400 TCR-A1 or 4400 TCR-A2 of Example 2 or the 4400 TCR-B1, 4400 TCR-B2. Target cells were DC (i) transfected with full length G13D KRAS mRNA (G13D FL) or the corresponding full length WT KRAS mRNA (WT FL); (ii) pulsed with the G13D 25-mer peptide (G13D Mut LP) or the corresponding WT 25-mer peptide (G13 WT LP) of Example 1. Transfected cells co-cultured with DC treated with DMSO and Jurkat cells without TCR transfection served as negative controls.

[0020] Figure 6 is a graph showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay following co-culture of effector cells with target cells. Effector cells were healthy donor PBL independently transduced with the retroviral vector encoding the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, or 4400 TCR-N of Example 2 or the 4400 TCR-B1, or 4400 TCR-B2. Target cells were DC (i) transduced with full length G13D KRAS mRNA (G13D FL) or the corresponding full length WT KRAS protein (WT FL); (ii) pulsed with G13D 25-mer peptide (G13D Mut LP) or the corresponding WT 25-mer peptide (G13 WT LP) of Example 1; or (iii) pulsed with G12D 25-mer peptide (G12D Mut LP) or G12V 25-mer peptide (G12V Mut LP). Effector cells co-cultured with DC treated with DMSO served as a negative control. Effector cells treated with anti-CD3/CD28 antibodies served as a positive control.

[0021] Figures 7A-7B are graphs showing the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD8⁺ cells (Fig. 7A) or CD4⁺ cells (Fig. 7B) following co-culture of effector cells with target cells. Effector cells, target cells, and controls are as described for Figure 6.

[0022] Figure 8 is a graph showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay following co-culture of effector cells with target cells. HEK cells (target cells) were untransfected (control) or independently transfected with the HLA heterodimers shown (alpha and beta) and then were pulsed with the G13D 25-mer peptide of Example 1. The effector cells were healthy donor PBL independently transduced with the retroviral

vector encoding the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, or 4400 TCR-N of Example 2. Effector cells cultured in the presence of anti-CD3/anti-CD28 Dynabeads served as a positive control.

[0023] Figure 9 is a graph showing the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺ / mTCR⁺ cells following co-culture of effector cells with target cells. Effector cells, target cells, and controls are as described for Figure 8.

[0024] Figures 10A-10C are graphs showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay (Figure 10A) and the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺/mTCR⁺ cells (Fig. 10B) or CD8⁺/mTCR⁺ cells (Fig. 10C) following co-culture of effector cells with target cells. Effector cells were healthy donor PBL transduced with the retroviral vector of Example 2 encoding the 4400 TCR-A1. Target cells were DC pulsed with the indicated concentration (ng/mL) of G13D 25-mer peptide or the corresponding WT 25-mer peptide. Effector cells cultured alone (T only) served as a negative control. Effector cells treated with anti-CD3/CD28 antibodies served as a positive control.

[0025] Figures 11A-11C are graphs showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay (Figure 11A) and the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺/mTCR⁺ cells (Fig. 11B) or CD8⁺/mTCR⁺ cells (Fig. 11C) following co-culture of effector cells with target cells. Effector cells were healthy donor PBL transduced with the retroviral vector of Example 2 encoding the 4400 TCR-A2. Target cells and controls are as described for Figures 10A-10C.

[0026] Figures 12A-12C are graphs showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay (Figure 12A) and the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺/mTCR⁺ cells (Fig. 12B) or CD8⁺/mTCR⁺ cells (Fig. 12C) following co-culture of effector cells with target cells. Effector cells were healthy donor PBL transduced with the retroviral vector of Example 2 encoding the 4400 TCR-E. Target cells and controls are as described for Figures 10A-10C.

[0027] Figures 13A-13C are graphs showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay (Figure 13A) and the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺/mTCR⁺ cells (Fig. 13B) or CD8⁺/mTCR⁺ cells (Fig. 13C) following co-culture of effector cells with target cells.

Effector cells were healthy donor PBL transduced with the retroviral vector of Example 2 encoding the 4400 TCR-J. Target cells and controls are as described for Figures 10A-10C.

[0028] Figures 14A-14C are graphs showing the IFN- γ secretion (spots/3e4 cells) measured by ELISPOT assay (Figure 14A) and the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD4⁺/mTCR⁺ cells (Fig. 14B) or CD8⁺/mTCR⁺ cells (Fig. 14C) following co-culture of effector cells with target cells.

Effector cells were healthy donor PBL transduced with the retroviral vector of Example 2 encoding the 4400 TCR-N. Target cells and controls are as described for Figures 10A-10C.

[0029] Figure 15 is a graph showing the luminescence ratio obtained upon co-culture of effector cells with target cells. Effector cells were a Jurkat cell line stably expressing luciferase under the transcriptional control of an NFAT promotor and also stably expressing the CD4 co-receptor; these cells were virally transduced with one of the following TCRs: 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-A3, 4400 TCR-J, 4400 TCR-J2, 4400 TCR-E, 4400 TCR-N, 4400 TCR-N4, 4400 TCR-N12, or 4400 TCR-N13. Target cells were DC (i) transfected with full length G13D KRAS mRNA or the corresponding full length WT KRAS mRNA; (ii) pulsed with the G13D 25-mer peptide or the corresponding WT 25-mer peptide of Example 1. Mock transduction was used as a negative control. The luminescence ratio is the ratio of the luminescence value obtained with G13D full-length gene (FL) to the luminescence value obtained with WT FL or the ratio of the luminescence value obtained with G13D long peptide (LP) to the luminescence value obtained with G13 WT LP.

[0030] Figure 16 is a graph showing the luminescence ratio obtained following co-culture of effector cells with target cells. COS7 cells (target cells) were independently transfected with the HLA heterodimers shown in Figure 16 (alpha and beta) or with HLA DRA1 only and then were pulsed with the G13D 25-mer peptide of Example 1. The effector cells were the same as those described for Figure 15. Untransduced Jurkat cells co-cultured with the same target cells served as a negative control. The luminescence ratio is the ratio of the luminescence readout value obtained in the experiment to the average luminescence readout value obtained with the control.

[0031] Figures 17A-17J are graphs showing the luminescence ratio obtained following co-culture of effector cells with target cells. Effector cells were a Jurkat-NFAT-firefly luciferase CD4⁺/CD8⁺ cell line independently virally transduced with one of the following TCRs: 4400 TCR-A1 (17A), 4400 TCR-A2 (17B), 4400 TCR-A3 (17C), 4400 TCR-J (17D), 4400 TCR-J2 (17E), 4400 TCR-E (17F), 4400 TCR-N (17G), 4400 TCR-N4 (17H), 4400

TCR-N12 (17I), or 4400 TCR-N13 (17J). Target cells were DCs loaded with the G13D 25-mer peptide (triangles) or the corresponding WT 25-mer peptide (circles) at one of the concentrations (ng/mL) shown. The luminescence ratio is the ratio of the luminescence readout value obtained in the experiment to the luminescence readout value obtained with the same cells co-cultured with DC loaded with DMSO only.

[0032] Figure 17K is a graph showing the luminescence ratio obtained following a control experiment, namely the same experiment as that which was carried out for Figures 17A-17J, except that the Jurkat-NFAT firefly luciferase cell line was virally transduced with a control plasmid (a backbone plasmid without the gene encoding a TCR). Effector cells treated with PMA served as an additional control (stars). The luminescence ratio is as defined for Figures 17A-17J.

[0033] Figure 18 is a graph showing the luminescence ratio obtained following co-culture of effector cells with target cells. COS7 cells (target cells) were transfected with the HLA-DQA1*05:01 and HLA-DQB1*03:01 heterodimer and then were pulsed with the G13D 25-mer peptide of Example 1. Effector cells were a Jurkat-NFAT-firefly luciferase CD4⁺/CD8⁺ cell line independently virally transduced with 4400 TCR-C or 4400 TCR-20. The effector cells were co-cultured with untransfected COS7 loaded with G13D 25-mer peptide as a negative control. The luminescence ratio is the ratio of the luminescence readout value of the experiment to the luminescence readout value of the relevant control.

[0034] Figures 19A-19D are graphs showing the percentage of cells expressing one or both of 4-1BB and OX40 measured by FACS gated on CD8⁺ cells (Figs. 19B and 19D) or CD4⁺ cells (Figs. 19A and 19C) following co-culture of effector cells with target cells. Effector cells were PBL independently transduced with 4400 TCR-C (Figs. 19A-19B) or 4400 TCR-20 (Figs. 19C-19D). Target cells were DC pre-loaded with G13D 25-mer peptide (G13D) or the corresponding WT 25-mer peptide (WT) at one of the various concentrations shown.

DETAILED DESCRIPTION OF THE INVENTION

[0035] 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.

[0036] 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: 51. WT KRAS variant B has the amino acid sequence of SEQ ID NO: 52. 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).

[0037] 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: 53.

[0038] 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: 54.

[0039] 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 13 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 13 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.

[0040] 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.

[0041] 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 13 with aspartic acid, wherein position 13 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: 51 or 52), WT HRAS protein (SEQ ID NO: 53), or WT NRAS protein (SEQ ID NO: 54) 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 13 of each of WT KRAS, WT HRAS, and WT NRAS protein is the same, namely, glycine.

[0042] The mutated human RAS amino acid sequence has a substitution of glycine at position 13 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 G13D mutation.

[0043] 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 13), 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 13 is defined herein by reference to the WT full-length RAS protein (namely, any one of SEQ ID NOs: 51-54) 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: 51-54, the term “G13” refers to the glycine normally present at position 13 of any one of SEQ ID NOs: 51-54, and “G13D” indicates that the glycine normally present at position 13 of any one of SEQ ID NOs: 51-54 is replaced by aspartic acid. For example, when a particular example of a RAS amino acid sequence is, e.g., TEYKLVVVGAGGVGKSALTIQLI (SEQ ID NO: 113) (an exemplary WT KRAS peptide corresponding to contiguous amino acid residues 2 to 24 of

SEQ ID NO: 51), “G13D” refers to a substitution of the underlined glycine in SEQ ID NO: 113 with aspartic acid, even though the actual position of the underlined glycine in SEQ ID NO: 113 is 12. Human RAS amino acid sequences with the G13D mutation are hereinafter referred to as “G13D RAS”.

[0044] Examples of full-length RAS proteins with the G13D mutation are set forth in Table 1 below.

TABLE 1

Mutated Full-Length RAS Protein	SEQ ID NO:
G13D KRAS variant A	55
G13D KRAS variant B	56
G13D HRAS	57
G13D NRAS	58

[0045] In an embodiment of the invention, the TCR has antigenic specificity for a RAS peptide with the G13D mutation described above, wherein the G13D RAS peptide has any length. In an embodiment of the invention, the G13D RAS peptide has any length suitable for binding to any of the HLA Class II molecules described herein. For example, the TCR may have antigenic specificity for a RAS peptide with the G13D mutation, the RAS peptide having a length of about 11 to about 30 amino acid residues, about 12 to about 24 amino acid residues, or about 18 to about 20 amino acid residues. The G13D RAS peptide may comprise any contiguous amino acid residues of mutated RAS protein which include the G13D mutation. In an embodiment of the invention, the TCR may have antigenic specificity for a RAS peptide with the G13D mutation, the mutated RAS peptide having a length of about 30 amino acid residues, about 29 amino acid residues, about 28 amino acid residues, about 27 amino acid residues, about 26 amino acid residues, about 25 amino acid residues, about 24 amino acid residues, about 23 amino acid residues, about 22 amino acid residues, about 21 amino acid residues, about 20 amino acid residues, about 19 amino acid residues, about 18 amino acid residues, about 17 amino acid residues, about 16 amino acid residues, about 15 amino acid residues, about 14 amino acid residues, about 13 amino acid residues, about 12 amino acid residues, about 11 amino acid residues, or a range of any two of the foregoing values. An example of a specific peptide with the G13D mutation, which may be recognized by the inventive TCRs, is MTEYKLVVVGAGDVGKSALTIQLI (SEQ ID NO: 106). Another example of a specific peptide with the G13D mutation, which may be recognized by

the inventive TCRs, is MTEYKLVVVGAGDVGKSALTILQI (SEQ ID NO: 252). In an embodiment of the invention, the TCR has antigenic specificity for the mutated human RAS amino acid sequence of SEQ ID NO: 106. In another embodiment of the invention, the TCR has antigenic specificity for the mutated human RAS amino acid sequence of SEQ ID NO: 252. In an embodiment of the invention, the TCR does not have antigenic specificity for the wild-type human RAS amino acid sequence of MTEYKLVVVGAGGVGKSALTILQI (SEQ ID NO: 107). In another embodiment of the invention, the TCR does not have antigenic specificity for the wild-type human RAS amino acid sequence of MTEYKLVVVGAGGVGKSALTILQI (SEQ ID NO: 253).

[0046] In an embodiment of the invention, the inventive TCRs are able to recognize G13D RAS presented by an HLA Class II molecule. In this regard, the TCR may elicit an immune response upon binding to G13D RAS within the context of an HLA Class II molecule. The inventive TCRs are able to recognize G13D RAS that is presented by an HLA Class II molecule and may bind to the HLA Class II molecule in addition to G13D RAS.

[0047] In an embodiment of the invention, the HLA Class II molecule is an HLA-DQ heterodimer. The HLA-DQ heterodimer is a cell surface receptor including an α chain and a β chain. The HLA-DQ α chain is encoded by the HLA-DQA1 gene. HLA-DQA1 alleles may include DQA1*01:01, DQA1*01:02, DQA1*01:03, DQA1*01:04, DQA1*02:01, DQA1*03:01, DQA1*03:02, DQA1*03:03, DQA1*04:01, DQA1*05:01, DQA1*05:05, and DQA1*06:01. The HLA-DQ β chain is encoded by the HLA-DQB1 gene. HLA-DQB1 alleles may include HLA-DQB1*02:01, HLA-DQB1*02:02, HLA-DQB1*02:03, HLA-DQB1*03:01, HLA-DQB1*03:02, HLA-DQB1*03:03, HLA-DQB1*03:04, HLA-DQB1*03:05, HLA-DQB1*04:01, HLA-DQB1*04:02, HLA-DQB1*05:01, HLA-DQB1*05:02, HLA-DQB1*05:03, HLA-DQB1*05:04, HLA-DQB1*06:01, HLA-DQB1*06:02, HLA-DQB1*06:03, HLA-DQB1*06:04, HLA-DQB1*06:05, and HLA-DQB1*06:09. In an embodiment of the invention, the HLA Class II molecule is an HLA-DQA1:HLA-DQB1 heterodimer. In an especially preferred embodiment, the HLA Class II molecule is expressed by the HLA-DQA1*05:01:HLA-DQB1*03:01 alleles (namely, an HLA-DQA1*05:01:HLA-DQB1*03:01 heterodimer).

[0048] 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. G13D 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, for example, by minimizing or eliminating, toxicity. Moreover, because the G13D mutation is likely to occur in the early stages of tumorigenesis, the G13D RAS mutation may be expressed on substantially all of a patient's cancer cells. The inventive TCRs may, advantageously, successfully treat or prevent G13D 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 G13D 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 G13D RAS and any of the HLA-DQ heterodimers described herein, pulsed with a G13D RAS peptide, or a combination thereof). KRAS mutations are found in about 30% of all cancer patients. The G13D RAS mutation is found in about 13% of cancer patients with a KRAS mutation. Moreover, the HLA-DQA1*05:01:HLA-DQB1*03:01 allele combination is expressed by about 35% of humans with Caucasian ethnicity in the United States and is also commonly expressed by humans of other ethnicities. Accordingly, the inventive TCRs may increase the number of immunotherapy-eligible cancer patients to include those patients that express the HLA-DQA1*05:01:HLA-DQB1*03:01 allele combination 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 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.

[0049] The phrase “antigenic specificity,” as used herein, means that the TCR can specifically bind to and immunologically recognize G13D RAS with high avidity. For example, a TCR may be considered to have “antigenic specificity” for G13D RAS if about 1×10^4 to about 1×10^5 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 II molecule positive target cells pulsed with a low concentration of G13D 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 II molecule positive target cells into which a nucleotide sequence encoding G13D RAS has been introduced such that the target cell expresses G13D RAS. Cells expressing the inventive TCRs may also secrete IFN- γ upon co-culture with antigen-negative, HLA Class II molecule positive target cells pulsed with higher concentrations of G13D RAS peptide. The HLA Class II molecule may be any of the HLA Class II molecules described herein.

[0050] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for G13D 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 II molecule positive target cells pulsed with a low concentration of G13D RAS peptide or (b) antigen-negative, HLA Class II molecule positive target cells into which a nucleotide sequence encoding G13D RAS has been introduced such that the target cell expresses G13D 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 II molecule positive target cells pulsed with the same concentration of an irrelevant peptide (e.g., some other peptide with a different sequence from the G13D RAS peptide) or (b) antigen-negative, HLA Class II 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 II molecule positive target cells pulsed with the same concentration of G13D RAS peptide or (b) antigen-negative, HLA Class II molecule positive target cells into which a nucleotide sequence encoding G13D RAS has been introduced such that the target cell expresses G13D RAS. The HLA Class II molecule expressed by the target cells of the negative control would be the same HLA Class II molecule expressed by the target cells that are co-cultured with the T cells being tested. The HLA Class II molecule may be any of the HLA Class II molecules described herein. IFN- γ secretion may be measured by methods known in the art such as, for example, enzyme-linked immunosorbent assay (ELISA).

[0051] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for G13D 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 II molecule positive target cells pulsed with a low concentration of G13D RAS peptide or (b) antigen-negative, HLA Class II molecule positive target cells into which a nucleotide

sequence encoding G13D RAS has been introduced such that the target cell expresses G13D RAS as compared to the numbers of negative control T cells that secrete IFN- γ . The HLA Class II 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.

[0052] Alternatively or additionally, a TCR may be considered to have “antigenic specificity” for G13D 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 G13D 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.).

[0053] 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 G13D RAS. In some embodiments, the TCR is non-naturally occurring.

[0054] 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 4400 TCR-A1), a CDR2 comprising the amino acid sequence of SEQ ID NO: 2 (CDR2 of α chain of 4400 TCR-A1), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 3 (CDR3 of α chain of 4400 TCR-A1), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 4 (CDR1 of β chain of 4400 TCR-A1), a CDR2 comprising the amino acid sequence of SEQ ID NO: 5 (CDR2 of β chain of 4400 TCR-A1), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 6 (CDR3 of β chain of 4400 TCR-A1).

[0055] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 11 (CDR1 of α chain of 4400 TCR-A2), a CDR2 comprising the amino acid sequence of SEQ ID NO: 12 (CDR2 of α chain of 4400 TCR-A2), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 13 (CDR3 of α chain of 4400 TCR-A2), and a second polypeptide chain

comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 14 (CDR1 of β chain of 4400 TCR-A2), a CDR2 comprising the amino acid sequence of SEQ ID NO: 15 (CDR2 of β chain of 4400 TCR-A2), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 16 (CDR3 of β chain of 4400 TCR-A2).

[0056] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 21 (CDR1 of α chain of 4400 TCR-E), a CDR2 comprising the amino acid sequence of SEQ ID NO: 22 (CDR2 of α chain of 4400 TCR-E), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 23 (CDR3 of α chain of 4400 TCR-E), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 24 (CDR1 of β chain of 4400 TCR-E), a CDR2 comprising the amino acid sequence of SEQ ID NO: 25 (CDR2 of β chain of 4400 TCR-E), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 26 (CDR3 of β chain of 4400 TCR-E).

[0057] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 31 (CDR1 of α chain of 4400 TCR-J), a CDR2 comprising the amino acid sequence of SEQ ID NO: 32 (CDR2 of α chain of 4400 TCR-J), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 33 (CDR3 of α chain of 4400 TCR-J), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 34 (CDR1 of β chain of 4400 TCR-J), a CDR2 comprising the amino acid sequence of SEQ ID NO: 35 (CDR2 of β chain of 4400 TCR-J), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 36 (CDR3 of β chain of 4400 TCR-J).

[0058] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 41 (CDR1 of α chain of 4400 TCR-N), a CDR2 comprising the amino acid sequence of SEQ ID NO: 42 (CDR2 of α chain of 4400 TCR-N), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 43 (CDR3 of α chain of 4400 TCR-N), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 44 (CDR1 of β chain of 4400 TCR-N), a CDR2 comprising the amino acid sequence of SEQ ID NO: 45 (CDR2 of β chain of 4400 TCR-N), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 46 (CDR3 of β chain of 4400 TCR-N).

[0059] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 119 (CDR1

of α chain of 4400 TCR-A3), a CDR2 comprising the amino acid sequence of SEQ ID NO: 120 (CDR2 of α chain of 4400 TCR-A3), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 121 (CDR3 of α chain of 4400 TCR-A3), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 122 (CDR1 of β chain of 4400 TCR-A3), a CDR2 comprising the amino acid sequence of SEQ ID NO: 123 (CDR2 of β chain of 4400 TCR-A3), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 124 (CDR3 of β chain of 4400 TCR-A3).

[0060] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 129 (CDR1 of α chain of 4400 TCR-J2), a CDR2 comprising the amino acid sequence of SEQ ID NO: 130 (CDR2 of α chain of 4400 TCR-J2), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 131 (CDR3 of α chain of 4400 TCR-J2), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 132 (CDR1 of β chain of 4400 TCR-J2), a CDR2 comprising the amino acid sequence of SEQ ID NO: 133 (CDR2 of β chain of 4400 TCR-J2), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 134 (CDR3 of β chain of 4400 TCR-J2).

[0061] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 139 (CDR1 of α chain of 4400 TCR-N4), a CDR2 comprising the amino acid sequence of SEQ ID NO: 140 (CDR2 of α chain of 4400 TCR-N4), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 141 (CDR3 of α chain of 4400 TCR-N4), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 142 (CDR1 of β chain of 4400 TCR-N4), a CDR2 comprising the amino acid sequence of SEQ ID NO: 143 (CDR2 of β chain of 4400 TCR-N4), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 144 (CDR3 of β chain of 4400 TCR-N4).

[0062] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 149 (CDR1 of α chain of 4400 TCR-N12), a CDR2 comprising the amino acid sequence of SEQ ID NO: 150 (CDR2 of α chain of 4400 TCR-N12), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 151 (CDR3 of α chain of 4400 TCR-N12), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 152 (CDR1 of β chain of 4400 TCR-N12), a CDR2 comprising the amino acid sequence of SEQ ID NO: 153

(CDR2 of β chain of 4400 TCR-N12), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 154 (CDR3 of β chain of 4400 TCR-N12).

[0063] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 159 (CDR1 of α chain of 4400 TCR-N13), a CDR2 comprising the amino acid sequence of SEQ ID NO: 160 (CDR2 of α chain of 4400 TCR-N13), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 161 (CDR3 of α chain of 4400 TCR-N13), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 162 (CDR1 of β chain of 4400 TCR-N13), a CDR2 comprising the amino acid sequence of SEQ ID NO: 163 (CDR2 of β chain of 4400 TCR-N13), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 164 (CDR3 of β chain of 4400 TCR-N13).

[0064] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 169 (CDR1 of α chain of 4400 TCR-C), a CDR2 comprising the amino acid sequence of SEQ ID NO: 170 (CDR2 of α chain of 4400 TCR-C), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171 (CDR3 of α chain of 4400 TCR-C), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 172 (CDR1 of β chain of 4400 TCR-C), a CDR2 comprising the amino acid sequence of SEQ ID NO: 173 (CDR2 of β chain of 4400 TCR-C), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 174 (CDR3 of β chain of 4400 TCR-C).

[0065] In another embodiment of the invention, the TCR comprises a first polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 179 (CDR1 of α chain of 4400 TCR-20), a CDR2 comprising the amino acid sequence of SEQ ID NO: 180 (CDR2 of α chain of 4400 TCR-20), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 181 (CDR3 of α chain of 4400 TCR-20), and a second polypeptide chain comprising a CDR1 comprising the amino acid sequence of SEQ ID NO: 182 (CDR1 of β chain of 4400 TCR-20), a CDR2 comprising the amino acid sequence of SEQ ID NO: 183 (CDR2 of β chain of 4400 TCR-20), and a CDR3 comprising the amino acid sequence of SEQ ID NO: 184 (CDR3 of β chain of 4400 TCR-20).

[0066] In this regard, the inventive TCR can comprise any one or more of the amino acid sequences selected from the group consisting of SEQ ID NOs: 1-6, 11-16, 21-26, 31-36, and 41-46. 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, (c) all of SEQ ID NOs: 1-6, (d) all of

SEQ ID NOs: 11-13, (e) all of SEQ ID NOs: 14-16, (f) all of SEQ ID NOs: 11-16, (g) all of SEQ ID NOs: 21-23, (h) all of SEQ ID NOs: 24-26, (i) all of SEQ ID NOs: 21-26, (j) all of SEQ ID NOs: 31-33, (k) all of SEQ ID NOs: 34-36, (l) all of SEQ ID NOs: 31-36, (m) all of SEQ ID NOs: 41-43, (n) all of SEQ ID NOs: 44-46, (o) all of SEQ ID NOs: 41-46, (p) all of SEQ ID NOs: 119-121, (q) all of SEQ ID NOs: 122-124, (r) all of SEQ ID NOs: 119-124, (s) all of SEQ ID NOs: 129-131, (t) all of SEQ ID NOs: 132-134, (u) all of SEQ ID NOs: 129-134, (v) all of SEQ ID NOs: 139-141, (w) all of SEQ ID NOs: 142-144, (x) all of SEQ ID NOs: 139-144, (y) all of SEQ ID NOs: 149-151, (z) all of SEQ ID NOs: 152-154, (aa) all of SEQ ID NOs: 149-154, (bb) all of SEQ ID NOs: 159-161, (cc) all of SEQ ID NOs: 162-164, (dd) all of SEQ ID NOs: 159-164, (ee) all of SEQ ID NOs: 169-171, (ff) all of SEQ ID NOs: 172-174, (gg) all of SEQ ID NOs: 169-174, (hh) all of SEQ ID NOs: 179-181, (ii) all of SEQ ID NOs: 182-184, or (jj) all of SEQ ID NOs: 179-184. In an especially preferred embodiment, the TCR comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-6, (b) all of SEQ ID NOs: 11-16, (c) all of SEQ ID NOs: 21-26, (d) all of SEQ ID NOs: 31-36, (e) all of SEQ ID NOs: 41-46, (f) all of SEQ ID NOs: 119-124, (g) all of SEQ ID NOs: 129-134, (h) all of SEQ ID NOs: 139-144, (i) all of SEQ ID NOs: 149-154, (j) all of SEQ ID NOs: 159-164, (k) all of SEQ ID NOs: 169-174, or (l) all of SEQ ID NOs: 179-184.

[0067] 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 comprise the amino acid sequence of: (1) SEQ ID NO: 7 (predicted sequence of variable region of α chain of 4400 TCR-A1 without N-terminal signal peptide); (2) SEQ ID NO: 8 (predicted sequence of variable region of β chain of 4400 TCR-A1 without N-terminal signal peptide); (3) SEQ ID NO: 9 (variable region of α chain of 4400 TCR-A1 with N-terminal signal peptide); (4) SEQ ID NO: 10 (variable region of β chain of 4400 TCR-A1 with N-terminal signal peptide); (5) SEQ ID NO: 17 (predicted sequence of variable region of α chain of 4400 TCR-A2 without N-terminal signal peptide); (6) SEQ ID NO: 18 (predicted sequence of variable region of β chain of 4400 TCR-A2 without N-terminal signal peptide); (7) SEQ ID NO: 19 (variable region of α chain of 4400 TCR-A2 with N-terminal signal peptide); (8) SEQ ID NO: 20 (variable region of β chain of 4400 TCR-A2 with N-terminal signal peptide); (9) SEQ ID NO: 27 (predicted sequence of variable region of α chain of 4400 TCR-E without N-terminal signal peptide); (10) SEQ ID NO: 28 (predicted sequence of variable region of β chain of 4400 TCR-E without N-terminal signal peptide); (11) SEQ ID NO: 29 (variable region of α chain of 4400 TCR-E with N-terminal signal peptide); (12) SEQ

ID NO: 30 (variable region of β chain of 4400 TCR-E with N-terminal signal peptide); (13) SEQ ID NO: 37 (predicted sequence of variable region of α chain of 4400 TCR-J without N-terminal signal peptide); (14) SEQ ID NO: 38 (predicted sequence of variable region of β chain of 4400 TCR-J without N-terminal signal peptide); (15) SEQ ID NO: 39 (variable region of α chain of 4400 TCR-J with N-terminal signal peptide); (16) SEQ ID NO: 40 (variable region of β chain of 4400 TCR-J with N-terminal signal peptide); (17) SEQ ID NO: 47 (predicted sequence of variable region of α chain of 4400 TCR-N without N-terminal signal peptide); (18) SEQ ID NO: 48 (predicted sequence of variable region of β chain of 4400 TCR-N without N-terminal signal peptide); (19) SEQ ID NO: 49 (variable region of α chain of 4400 TCR-N with N-terminal signal peptide); (20) SEQ ID NO: 50 (variable region of β chain of 4400 TCR-N with N-terminal signal peptide); (21) SEQ ID NO: 125 (predicted sequence of variable region of α chain of 4400 TCR-A3 without N-terminal signal peptide); (22) SEQ ID NO: 126 (predicted sequence of variable region of β chain of 4400 TCR-A3 without N-terminal signal peptide); (23) SEQ ID NO: 127 (variable region of α chain of 4400 TCR-A3 with N-terminal signal peptide); (24) SEQ ID NO: 128 (variable region of β chain of 4400 TCR-A3 with N-terminal signal peptide); (25) SEQ ID NO: 135 (predicted sequence of variable region of α chain of 4400 TCR-J2 without N-terminal signal peptide); (26) SEQ ID NO: 136 (predicted sequence of variable region of β chain of 4400 TCR-J2 without N-terminal signal peptide); (27) SEQ ID NO: 137 (variable region of α chain of 4400 TCR-J2 with N-terminal signal peptide); (28) SEQ ID NO: 138 (variable region of β chain of 4400 TCR-J2 with N-terminal signal peptide); (29) SEQ ID NO: 145 (predicted sequence of variable region of α chain of 4400 TCR-N4 without N-terminal signal peptide); (30) SEQ ID NO: 146 (predicted sequence of variable region of β chain of 4400 TCR-N4 without N-terminal signal peptide); (31) SEQ ID NO: 147 (variable region of α chain of 4400 TCR-N4 with N-terminal signal peptide); (32) SEQ ID NO: 148 (variable region of β chain of 4400 TCR-N4 with N-terminal signal peptide); (33) SEQ ID NO: 155 (predicted sequence of variable region of α chain of 4400 TCR-N12 without N-terminal signal peptide); (34) SEQ ID NO: 156 (predicted sequence of variable region of β chain of 4400 TCR-N12 without N-terminal signal peptide); (35) SEQ ID NO: 157 (variable region of α chain of 4400 TCR-N12 with N-terminal signal peptide); (36) SEQ ID NO: 158 (variable region of β chain of 4400 TCR-N12 with N-terminal signal peptide); (37) SEQ ID NO: 165 (predicted sequence of variable region of α chain of 4400 TCR-N13 without N-terminal signal peptide); (38) SEQ ID NO: 166 (predicted sequence of variable region of β chain of 4400 TCR-N13 without N-

terminal signal peptide); (39) SEQ ID NO: 167 (variable region of α chain of 4400 TCR-N13 with N-terminal signal peptide); (40) SEQ ID NO: 168 (variable region of β chain of 4400 TCR-N13 with N-terminal signal peptide); (41) SEQ ID NO: 175 (predicted sequence of variable region of α chain of 4400 TCR-C without N-terminal signal peptide); (42) SEQ ID NO: 176 (predicted sequence of variable region of β chain of 4400 TCR-C without N-terminal signal peptide); (43) SEQ ID NO: 177 (variable region of α chain of 4400 TCR-C with N-terminal signal peptide); (44) SEQ ID NO: 178 (variable region of β chain of 4400 TCR-C with N-terminal signal peptide); (45) SEQ ID NO: 185 (predicted sequence of variable region of α chain of 4400 TCR-20 without N-terminal signal peptide); (46) SEQ ID NO: 186 (predicted sequence of variable region of β chain of 4400 TCR-20 without N-terminal signal peptide); (47) SEQ ID NO: 187 (variable region of α chain of 4400 TCR-20 with N-terminal signal peptide); (48) SEQ ID NO: 188 (variable region of β chain of 4400 TCR-20 with N-terminal signal peptide); (49) both of SEQ ID NOs: 7 and 8; (50) both of SEQ ID NOs: 9 and 10; (51) both of SEQ ID NOs: 17 and 18; (52) both of SEQ ID NOs: 19 and 20; (53) both of SEQ ID NOs: 27 and 28; (54) both of SEQ ID NOs: 29 and 30; (55) both of SEQ ID NOs: 37 and 38; (56) both of SEQ ID NOs: 39 and 40; (57) both of SEQ ID NOs: 47 and 48; (58) both of SEQ ID NOs: 49 and 50; (59) both of SEQ ID NOs: 125 and 126; (60) both of SEQ ID NOs: 127 and 128; (61) both of SEQ ID NOs: 135 and 136; (62) both of SEQ ID NOs: 137 and 138; (63) both of SEQ ID NOs: 145 and 146; (64) both of SEQ ID NOs: 147 and 148; (65) both of SEQ ID NOs: 155 and 156; (66) both of SEQ ID NOs: 157 and 158; (67) both of SEQ ID NOs: 165 and 166; (68) both of SEQ ID NOs: 167 and 168; (69) both of SEQ ID NOs: 175 and 176; (70) both of SEQ ID NOs: 177 and 178; (71) both of SEQ ID NOs: 185 and 186; or (72) both of SEQ ID NOs: 187 and 188. Preferably, the TCR comprises the amino acid sequences of (i) both of SEQ ID NOs: 7 and 8, (ii) both of SEQ ID NOs: 9 and 10, (iii) both of SEQ ID NOs: 17 and 18, (iv) both of SEQ ID NOs: 19 and 20, (v) both of SEQ ID NOs: 27 and 28, (vi) both of SEQ ID NOs: 29 and 30, (vii) both of SEQ ID NOs: 37 and 38, (viii) both of SEQ ID NOs: 39 and 40, (ix) both of SEQ ID NOs: 47 and 48, (x) both of SEQ ID NOs: 49 and 50, (xi) both of SEQ ID NOs: 125 and 126, (xii) both of SEQ ID NOs: 127 and 128, (xiii) both of SEQ ID NOs: 135 and 136, (xiv) both of SEQ ID NOs: 137 and 138, (xv) both of SEQ ID NOs: 145 and 146, (xvi) both of SEQ ID NOs: 147 and 148, (xvii) both of SEQ ID NOs: 155 and 156, (xviii) both of SEQ ID NOs: 157 and 158, (xix) both of SEQ ID NOs: 165 and 166, (xx) both of SEQ ID NOs: 167 and 168, (xxi) both

of SEQ ID NOs: 175 and 176, (xxii) both of SEQ ID NOs: 177 and 178, (xxiii) both of SEQ ID NOs: 185 and 186, or (xxiv) both of SEQ ID NOs: 187 and 188.

[0068] 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.

[0069] 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 13 with aspartic acid. 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 the 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: 63 (WT murine α chain constant region), SEQ ID NO: 64 (WT murine β chain constant region), or both SEQ ID NOs: 63 and 64. Preferably, the inventive TCR comprises the amino acid sequences of both of SEQ ID NOs: 63 and 64. 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 may comprise the amino acid sequences of: (a) all of SEQ ID NOs: 1-3 and 63, (b) all of SEQ ID NOs: 4-6 and 64, (c) all of SEQ ID NOs: 1-6 and 63-64, (d) all of SEQ ID NOs: 11-13 and 63, (e) all of SEQ ID NOs: 14-16 and 64, (f) all of SEQ ID NOs: 11-16 and 63-64, (g) all of SEQ ID NOs: 21-23 and 63, (h) all of SEQ ID NOs: 24-26 and 64, (i) all of SEQ ID NOs: 21-26 and 63-64, (j) all of SEQ ID NOs: 31-33 and 63, (k) all of SEQ ID NOs: 34-36 and 64, (l) all of SEQ ID NOs: 31-36 and 63-64, (m) all of SEQ ID NOs: 41-43 and 63, (n) all of SEQ ID NOs: 44-46 and 64, (o) all of SEQ ID NOs: 41-46 and 63-64, (p) all of SEQ ID NOs: 119-121 and 63, (q) all of SEQ ID NOs: 122-124 and 64, (r) all of SEQ ID NOs: 119-124 and 63-64, (s) all of SEQ ID NOs: 129-131 and 63,

(t) all of SEQ ID NOs: 132-134 and 64, (u) all of SEQ ID NOs: 129-134 and 63-64, (v) all of SEQ ID NOs: 139-141 and 63, (w) all of SEQ ID NOs: 142-144 and 64, (x) all of SEQ ID NOs: 139-144 and 63-64, (y) all of SEQ ID NOs: 149-151 and 63, (z) all of SEQ ID NOs: 152-154 and 64, (aa) all of SEQ ID NOs: 149-154 and 63-64, (bb) all of SEQ ID NOs: 159-161 and 63, (cc) all of SEQ ID NOs: 162-164 and 64, (dd) all of SEQ ID NOs: 159-164 and 63-64, (ee) all of SEQ ID NOs: 169-171 and 63, (ff) all of SEQ ID NOs: 172-174 and 64, (gg) all of SEQ ID NOs: 169-174 and 63-64, (hh) all of SEQ ID NOs: 179-181 and 63, (ii) all of SEQ ID NOs: 182-184 and 64, or (jj) all of SEQ ID NOs: 179-184 and 63-64.

[0070] 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 may comprise the amino acid sequences of: (1) both of SEQ ID NOs: 7 and 63, (2) both of SEQ ID NOs: 8 and 64, (3) both of SEQ ID NOs: 9 and 63, (4) both of SEQ ID NOs: 10 and 64, (5) both of SEQ ID NOs: 17 and 63, (6) both of SEQ ID NOs: 18 and 64, (7) both of SEQ ID NOs: 19 and 63, (8) both of SEQ ID NOs: 20 and 64, (9) both of SEQ ID NOs: 27 and 63, (10) both of SEQ ID NOs: 28 and 64, (11) both of SEQ ID NOs: 29 and 63, (12) both of SEQ ID NOs: 30 and 64, (13) both of SEQ ID NOs: 37 and 63, (14) both of SEQ ID NOs: 38 and 64, (15) both of SEQ ID NOs: 39 and 63, (16) both of SEQ ID NOs: 40 and 64, (17) both of SEQ ID NOs: 47 and 63, (17) both of SEQ ID NOs: 48 and 64, (19) both of SEQ ID NOs: 49 and 63, (20) both of SEQ ID NOs: 50 and 64, (21) both of SEQ ID NOs: 125 and 63, both of (22) SEQ ID NOs: 126 and 64, (23) both of SEQ ID NOs: 127 and 63, (24) both of SEQ ID NOs: 128 and 64, (25) both of SEQ ID NOs: 135 and 63, (26) both of SEQ ID NOs: 136 and 64, (27) both of SEQ ID NOs: 137 and 63, (28) both of SEQ ID NOs: 138 and 64, (29) both of SEQ ID NOs: 145 and 63, (30) both of SEQ ID NOs: 146 and 64, (31) both of SEQ ID NOs: 147 and 63, (32) both of SEQ ID NOs: 148 and 64, (33) both of SEQ ID NOs: 155 and 63, (34) both of SEQ ID NOs: 156 and 64, (35) both of SEQ ID NOs: 157 and 63, (36) both of SEQ ID NOs: 158 and 64, (37) both of SEQ ID NOs: 165 and 63, (38) both of SEQ ID NOs: 166 and 64, (39) both of SEQ ID NOs: 167 and 63, (40) both of SEQ ID NOs: 168 and 64, (41) both of SEQ ID NOs: 175 and 63, (42) both of SEQ ID NOs: 176 and 64, (43) both of SEQ ID NOs: 177 and 63, (44) both of SEQ ID NOs: 178 and 64, (45) both of SEQ ID NOs: 185 and 63, (46) both of SEQ ID NOs: 186 and 64, (47) both of SEQ ID NOs: 187 and 63, (48) both of SEQ ID NOs: 188 and 64, (49) all of SEQ ID NOs: 7-8 and 63-64, (50) all of SEQ ID NOs: 9-10 and 63-64, (51) all of SEQ ID NOs: 17-18 and 63-64, (52) all of SEQ ID

NOs: 19-20 and 63-64, (53) all of SEQ ID NOs: 27-28 and 63-64, (54) all of SEQ ID NOs: 29-30 and 63-64, (55) all of SEQ ID NOs: 37-38 and 63-64, (56) all of SEQ ID NOs: 39-40 and 63-64, (57) all of SEQ ID NOs: 47-48 and 63-64, (58) all of SEQ ID NOs: 49-50 and 63-64, (59) all of SEQ ID NOs: 125-126 and 63-64, (60) all of SEQ ID NOs: 127-128 and 63-64, (61) all of SEQ ID NOs: 135-136 and 63-64, (62) all of SEQ ID NOs: 137-138 and 63-64, (63) all of SEQ ID NOs: 145-146 and 63-64, (64) all of SEQ ID NOs: 147-148 and 63-64, (65) all of SEQ ID NOs: 155-156 and 63-64, (66) all of SEQ ID NOs: 157-158 and 63-64, (67) all of SEQ ID NOs: 165-166 and 63-64, (68) all of SEQ ID NOs: 167-168 and 63-64, (69) all of SEQ ID NOs: 175-176 and 63-64, (70) all of SEQ ID NOs: 177-178 and 63-64, (71) all of SEQ ID NOs: 185-186 and 63-64, or (72) all of SEQ ID NOs: 187-188 and 63-64.

[0071] In an embodiment of the invention, the TCR comprises a substituted constant region. In this regard, the TCR 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 G13D 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: 59 and 60, respectively, correspond with all or portions of the unsubstituted murine constant region amino acid sequences SEQ ID NOs: 63 and 64, respectively, with SEQ ID NO: 59 having one, two, three, or four amino acid substitution(s) when compared to SEQ ID NO: 63 and SEQ ID NO: 60 having one amino acid substitution when compared to SEQ ID NO: 64. In this regard, an embodiment of the invention provides a TCR comprising the amino acid sequences of (a) SEQ ID NO: 59 (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: 60 (constant region of β chain), wherein X at position 57 is

Ser or Cys; or (c) both of SEQ ID NOs: 59 and 60. In an embodiment of the invention, the TCR comprising SEQ ID NO: 59 does not comprise SEQ ID NO: 63 (unsubstituted murine constant region of α chain). In an embodiment of the invention, the TCR comprising SEQ ID NO: 60 does not comprise SEQ ID NO: 64 (unsubstituted murine constant region of β chain).

[0072] 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 may comprise (a) the amino acid sequence of SEQ ID NO: 65 (α chain of 4400 TCR-A1 with N-terminal signal peptide), wherein: (i) X at position 180 of SEQ ID NO: 65 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 65 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 65 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 65 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (b) the amino acid sequence of SEQ ID NO: 66 (β chain of 4400 TCR-A1 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 66 is Ser or Cys; (c) the amino acid sequences of both of SEQ ID NOs: 65 and 66; (d) the amino acid sequence of SEQ ID NO: 67 (predicted sequence of α chain of 4400 TCR-A1 without N-terminal signal peptide), wherein: (i) X at position 158 of SEQ ID NO: 67 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 67 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 67 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 67 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (e) the amino acid sequence of SEQ ID NO: 68 (predicted sequence of β chain of 4400 TCR-A1 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 68 is Ser or Cys; (f) the amino acid sequences of both of SEQ ID NOs: 67 and 68; (g) the amino acid sequence of SEQ ID NO: 69 (α chain of cysteine-substituted, LVL-modified 4400 TCR-A1 with N-terminal signal peptide); (h) the amino acid sequence of SEQ ID NO: 70 (β chain of cysteine-substituted, LVL-modified 4400 TCR-A1 with N-terminal signal peptide); (i) the amino acid sequence of SEQ ID NO: 71 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-A1 without N-terminal signal peptide); (j) the amino acid sequence of SEQ ID NO: 72 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-A1 without N-terminal signal peptide); (k) the amino acid sequences of both of SEQ ID NOs: 69 and 70; (l) the amino acid sequences of both of both of SEQ ID NOs: 71 and 72; (m) the amino acid sequence of SEQ ID NO: 73 (α chain of 4400 TCR-A2 with N-terminal signal peptide), wherein: (i) X at position 180 of SEQ ID NO: 73 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 73 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met,

or Trp; (iii) X at position 246 of SEQ ID NO: 73 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 73 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (n) the amino acid sequence of SEQ ID NO: 74 (β chain of 4400 TCR-A2 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 74 is Ser or Cys; (o) the amino acid sequences of both of SEQ ID NOs: 73 and 74; (p) the amino acid sequence of SEQ ID NO: 75 (predicted sequence of α chain of 4400 TCR-A2 without N-terminal signal peptide), wherein: (i) X at position 158 of SEQ ID NO: 75 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 75 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 75 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 75 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (q) the amino acid sequence of SEQ ID NO: 76 (predicted sequence of β chain of 4400 TCR-A2 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 76 is Ser or Cys; (r) the amino acid sequences of both of SEQ ID NOs: 75 and 76; (s) the amino acid sequence of SEQ ID NO: 77 (α chain of cysteine-substituted, LVL-modified 4400 TCR-A2 with N-terminal signal peptide); (t) the amino acid sequence of SEQ ID NO: 78 (β chain of cysteine-substituted, LVL-modified 4400 TCR-A2 with N-terminal signal peptide); (u) the amino acid sequence of SEQ ID NO: 79 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-A2 without N-terminal signal peptide); (v) the amino acid sequence of SEQ ID NO: 80 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-A2 without N-terminal signal peptide); (w) the amino acid sequences of both of SEQ ID NOs: 77 and 78; (x) the amino acid sequences of both of SEQ ID NOs: 79 and 80; (y) the amino acid sequence of SEQ ID NO: 81 (α chain of 4400 TCR-E with N-terminal signal peptide), wherein: (i) X at position 177 of SEQ ID NO: 81 is Thr or Cys; (ii) X at position 241 of SEQ ID NO: 81 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 243 of SEQ ID NO: 81 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 244 of SEQ ID NO: 81 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (z) the amino acid sequence of SEQ ID NO: 82 (β chain of 4400 TCR-E with N-terminal signal peptide), wherein X at position 189 of SEQ ID NO: 82 is Ser or Cys; (aa) the amino acid sequences of both of SEQ ID NOs: 81 and 82; (bb) the amino acid sequence of SEQ ID NO: 83 (predicted sequence of α chain of 4400 TCR-E without N-terminal signal peptide), wherein: (i) X at position 160 of SEQ ID NO: 83 is Thr or Cys; (ii) X at position 224 of SEQ ID NO: 83 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 226 of SEQ ID NO: 83 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 227 of SEQ ID NO: 83 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(cc) the amino acid sequence of SEQ ID NO: 84 (predicted sequence of β chain of 4400 TCR-E without N-terminal signal peptide), wherein X at position 170 of SEQ ID NO: 84 is Ser or Cys; (dd) the amino acid sequences of both of SEQ ID NOs: 83 and 84; (ee) the amino acid sequence of SEQ ID NO: 85 (α chain of cysteine-substituted, LVL-modified 4400 TCR-E with N-terminal signal peptide); (ff) the amino acid sequence of SEQ ID NO: 86 (β chain of cysteine-substituted, LVL-modified 4400 TCR-E with N-terminal signal peptide); (gg) the amino acid sequence of SEQ ID NO: 87 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-E without N-terminal signal peptide); (hh) the amino acid sequence of SEQ ID NO: 88 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-E without N-terminal signal peptide); (ii) the amino acid sequences of both of SEQ ID NOs: 85 and 86; (jj) the amino acid sequences of both of SEQ ID NOs: 87 and 88; (kk) the amino acid sequence of SEQ ID NO: 89 (α chain of 4400 TCR-J with N-terminal signal peptide), wherein: (i) X at position 183 of SEQ ID NO: 89 is Thr or Cys; (ii) X at position 247 of SEQ ID NO: 89 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 249 of SEQ ID NO: 89 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 250 of SEQ ID NO: 89 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ll) the amino acid sequence of SEQ ID NO: 90 (β chain of 4400 TCR-J with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 90 is Ser or Cys; (mm) the amino acid sequences of both of SEQ ID NOs: 89 and 90; (nn) the amino acid sequence of SEQ ID NO: 91 (predicted sequence of α chain of 4400 TCR-J without N-terminal signal peptide), wherein: (i) X at position 161 of SEQ ID NO: 91 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 91 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 91 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 91 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (oo) the amino acid sequence of SEQ ID NO: 92 (predicted sequence of β chain of 4400 TCR-J without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 92 is Ser or Cys; (pp) the amino acid sequences of both of SEQ ID NOs: 91 and 92; (qq) the amino acid sequence of SEQ ID NO: 93 (α chain of cysteine-substituted, LVL-modified 4400 TCR-J with N-terminal signal peptide); (rr) the amino acid sequence of SEQ ID NO: 94 (β chain of cysteine-substituted, LVL-modified 4400 TCR-J with N-terminal signal peptide); (ss) the amino acid sequence of SEQ ID NO: 95 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-J without N-terminal signal peptide); (tt) the amino acid sequence of SEQ ID NO: 96 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-J without N-terminal

signal peptide); (uu) the amino acid sequences of both of SEQ ID NOs: 93 and 94; (vv) the amino acid sequences of both of SEQ ID NOs: 95 and 96; (ww) the amino acid sequence of SEQ ID NO: 97 (α chain of 4400 TCR-N with N-terminal signal peptide), wherein: (i) X at position 178 of SEQ ID NO: 97 is Thr or Cys; (ii) X at position 242 of SEQ ID NO: 97 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 244 of SEQ ID NO: 97 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 245 of SEQ ID NO: 97 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (xx) the amino acid sequence of SEQ ID NO: 98 (β chain of 4400 TCR-N with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 98 is Ser or Cys; (yy) the amino acid sequences of both of SEQ ID NOs: 97 and 98; (zz) the amino acid sequence of SEQ ID NO: 99 (predicted sequence of α chain of 4400 TCR-N without N-terminal signal peptide), wherein: (i) X at position 157 of SEQ ID NO: 99 is Thr or Cys; (ii) X at position 221 of SEQ ID NO: 99 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 223 of SEQ ID NO: 99 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 224 of SEQ ID NO: 99 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (aaa) the amino acid sequence of SEQ ID NO: 100 (predicted sequence of β chain of 4400 TCR-N without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 100 is Ser or Cys; (bbb) the amino acid sequences of both of SEQ ID NOs: 99 and 100; (ccc) the amino acid sequence of SEQ ID NO: 101 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N with N-terminal signal peptide); (ddd) the amino acid sequence of SEQ ID NO: 102 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N with N-terminal signal peptide); (eee) the amino acid sequence of SEQ ID NO: 103 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N without N-terminal signal peptide); (fff) the amino acid sequence of SEQ ID NO: 104 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N without N-terminal signal peptide); (ggg) the amino acid sequences of both of SEQ ID NOs: 101 and 102; (hhh) the amino acid sequences of both of SEQ ID NOs: 103 and 104; (iii) the amino acid sequence of SEQ ID NO: 189 (α chain of 4400 TCR-A3 with N-terminal signal peptide), wherein: (i) X at position 176 of SEQ ID NO: 189 is Thr or Cys; (ii) X at position 240 of SEQ ID NO: 189 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 242 of SEQ ID NO: 189 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 243 of SEQ ID NO: 189 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (jjj) the amino acid sequence of SEQ ID NO: 190 (β chain of 4400 TCR-A3 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 190 is Ser or Cys; (kkk) the amino acid sequences of both of SEQ ID NOs: 189 and 190; (lll) the

amino acid sequence of SEQ ID NO: 191 (predicted sequence of α chain of 4400 TCR-A3 without N-terminal signal peptide), wherein: (i) X at position 157 of SEQ ID NO: 191 is Thr or Cys; (ii) X at position 221 of SEQ ID NO: 191 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 223 of SEQ ID NO: 191 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 224 of SEQ ID NO: 191 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (mmm) the amino acid sequence of SEQ ID NO: 192 (predicted sequence of β chain of 4400 TCR-A3 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 192 is Ser or Cys; (nnn) the amino acid sequences of both of SEQ ID NOs: 191 and 192; (ooo) the amino acid sequence of SEQ ID NO: 193 (α chain of cysteine-substituted, LVL-modified 4400 TCR-A3 with N-terminal signal peptide); (ppp) the amino acid sequence of SEQ ID NO: 194 (β chain of cysteine-substituted, LVL-modified 4400 TCR-A3 with N-terminal signal peptide); (qqq) the amino acid sequence of SEQ ID NO: 195 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-A3 without N-terminal signal peptide); (rrr) the amino acid sequence of SEQ ID NO: 196 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-A3 without N-terminal signal peptide); (sss) the amino acid sequences of both of SEQ ID NOs: 193 and 194; (ttt) the amino acid sequences of both of SEQ ID NOs: 195 and 196; (uuu) the amino acid sequence of SEQ ID NO: 197 (α chain of 4400 TCR-J2 with N-terminal signal peptide), wherein: (i) X at position 181 of SEQ ID NO: 197 is Thr or Cys; (ii) X at position 245 of SEQ ID NO: 197 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 247 of SEQ ID NO: 197 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 248 of SEQ ID NO: 197 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (vvv) the amino acid sequence of SEQ ID NO: 198 (β chain of 4400 TCR-J2 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 198 is Ser or Cys; (www) the amino acid sequences of both of SEQ ID NOs: 197 and 198; (xxx) the amino acid sequence of SEQ ID NO: 199 (predicted sequence of α chain of 4400 TCR-J2 without N-terminal signal peptide), wherein: (i) X at position 161 of SEQ ID NO: 199 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 199 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 199 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 199 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (yyy) the amino acid sequence of SEQ ID NO: 200 (predicted sequence of β chain of 4400 TCR-J2 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 200 is Ser or Cys; (zzz) the amino acid sequences of both of SEQ ID NOs: 199 and 200; (aaaa) the amino acid sequence of SEQ ID NO: 201 (α chain of

cysteine-substituted, LVL-modified 4400 TCR-J2 with N-terminal signal peptide); (bbbb) the amino acid sequence of SEQ ID NO: 202 (β chain of cysteine-substituted, LVL-modified 4400 TCR-J2 with N-terminal signal peptide); (cccc) the amino acid sequence of SEQ ID NO: 203 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-J2 without N-terminal signal peptide); (dddd) the amino acid sequence of SEQ ID NO: 204 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-J2 without N-terminal signal peptide); (eeee) the amino acid sequences of both of SEQ ID NOs: 201 and 202; (ffff) the amino acid sequences of both of SEQ ID NOs: 203 and 204; (gggg) the amino acid sequence of SEQ ID NO: 205 (α chain of 4400 TCR-N4 with N-terminal signal peptide), wherein: (i) X at position 184 of SEQ ID NO: 205 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 205 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 205 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 205 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (hhhh) the amino acid sequence of SEQ ID NO: 206 (β chain of 4400 TCR-N4 with N-terminal signal peptide), wherein X at position 190 of SEQ ID NO: 206 is Ser or Cys; (iiii) the amino acid sequences of both of SEQ ID NOs: 205 and 206; (jjjj) the amino acid sequence of SEQ ID NO: 207 (predicted sequence of α chain of 4400 TCR-N4 without N-terminal signal peptide), wherein: (i) X at position 163 of SEQ ID NO: 207 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 207 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 207 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 207 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (kkkk) the amino acid sequence of SEQ ID NO: 208 (predicted sequence of β chain of 4400 TCR-N4 without N-terminal signal peptide), wherein X at position 164 of SEQ ID NO: 208 is Ser or Cys; (llll) the amino acid sequences of both of SEQ ID NOs: 207 and 208; (mmmm) the amino acid sequence of SEQ ID NO: 209 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N4 with N-terminal signal peptide); (nnnn) the amino acid sequence of SEQ ID NO: 210 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N4 with N-terminal signal peptide); (oooo) the amino acid sequence of SEQ ID NO: 211 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N4 without N-terminal signal peptide); (pppp) the amino acid sequence of SEQ ID NO: 212 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N4 without N-terminal signal peptide); (qqqq) the amino acid sequences of both of SEQ ID NOs: 209 and 210; (rrrr) the amino acid sequences of both of SEQ ID NOs: 211 and 212; (ssss) the amino acid sequence of SEQ ID NO: 213 (α chain of 4400

TCR-N12 with N-terminal signal peptide), wherein: (i) X at position 183 of SEQ ID NO: 213 is Thr or Cys; (ii) X at position 247 of SEQ ID NO: 213 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 249 of SEQ ID NO: 213 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 250 of SEQ ID NO: 213 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (tttt) the amino acid sequence of SEQ ID NO: 214 (β chain of 4400 TCR-N12 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 214 is Ser or Cys; (uuuu) the amino acid sequences of both of SEQ ID NOs: 213 and 214; (vvvv) the amino acid sequence of SEQ ID NO: 215 (predicted sequence of α chain of 4400 TCR-N12 without N-terminal signal peptide), wherein: (i) X at position 161 of SEQ ID NO: 215 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 215 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 215 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 215 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (www) the amino acid sequence of SEQ ID NO: 216 (predicted sequence of β chain of 4400 TCR-N12 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 216 is Ser or Cys; (xxxx) the amino acid sequences of both of SEQ ID NOs: 215 and 216; (yyyy) the amino acid sequence of SEQ ID NO: 217 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N12 with N-terminal signal peptide); (zzzz) the amino acid sequence of SEQ ID NO: 218 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N12 with N-terminal signal peptide); (aaaaa) the amino acid sequence of SEQ ID NO: 219 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N12 without N-terminal signal peptide); (bbbbb) the amino acid sequence of SEQ ID NO: 220 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N12 without N-terminal signal peptide); (ccccc) the amino acid sequences of both of SEQ ID NOs: 217 and 218; (ddddd) the amino acid sequences of both of SEQ ID NOs: 219 and 220; (eeee) the amino acid sequence of SEQ ID NO: 221 (α chain of 4400 TCR-N13 with N-terminal signal peptide), wherein: (i) X at position 180 of SEQ ID NO: 221 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 221 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 221 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ffff) the amino acid sequence of SEQ ID NO: 222 (β chain of 4400 TCR-N13 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 222 is Ser or Cys; (ggggg) the amino acid sequences of both of SEQ ID NOs: 221 and 222; (hhhhh) the amino acid sequence of SEQ ID NO: 223 (predicted sequence of α chain of 4400 TCR-N13 without N-terminal signal

peptide), wherein: (i) X at position 158 of SEQ ID NO: 223 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 223 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 223 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iiii) the amino acid sequence of SEQ ID NO: 224 (predicted sequence of β chain of 4400 TCR-N13 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 224 is Ser or Cys; (jjjjj) the amino acid sequences of both of SEQ ID NOs: 223 and 224; (kkkkk) the amino acid sequence of SEQ ID NO: 225 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N13 with N-terminal signal peptide); (lllll) the amino acid sequence of SEQ ID NO: 226 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N13 with N-terminal signal peptide); (mmmmm) the amino acid sequence of SEQ ID NO: 227 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N13 without N-terminal signal peptide); (nnnnn) the amino acid sequence of SEQ ID NO: 228 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N13 without N-terminal signal peptide); (ooooo) the amino acid sequences of both of SEQ ID NOs: 225 and 226; (ppppp) the amino acid sequences of both of SEQ ID NOs: 227 and 228; (qqqqq) the amino acid sequence of SEQ ID NO: 229 (α chain of 4400 TCR-C with N-terminal signal peptide), wherein: (i) X at position 184 of SEQ ID NO: 229 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 229 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (rrrrr) the amino acid sequence of SEQ ID NO: 230 (β chain of 4400 TCR-C with N-terminal signal peptide), wherein X at position 189 of SEQ ID NO: 230 is Ser or Cys; (sssss) the amino acid sequences of both of SEQ ID NOs: 229 and 230; (ttttt) the amino acid sequence of SEQ ID NO: 231 (predicted sequence of α chain of 4400 TCR-C without N-terminal signal peptide), wherein: (i) X at position 163 of SEQ ID NO: 231 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 231 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 231 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (uuuuu) the amino acid sequence of SEQ ID NO: 232 (predicted sequence of β chain of 4400 TCR-C without N-terminal signal peptide), wherein X at position 170 of SEQ ID NO: 232 is Ser or Cys; (vvvvv) the amino acid sequences of both of SEQ ID NOs: 231 and 232; (wwwww) the amino acid sequence of SEQ ID NO: 233 (α chain of cysteine-substituted, LVL-modified 4400 TCR-C with N-terminal signal peptide);

(xxxxxx) the amino acid sequence of SEQ ID NO: 234 (β chain of cysteine-substituted, LVL-modified 4400 TCR-C with N-terminal signal peptide); (yyyyyy) the amino acid sequence of SEQ ID NO: 235 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-C without N-terminal signal peptide); (zzzzzz) the amino acid sequence of SEQ ID NO: 236 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-C without N-terminal signal peptide); (aaaaaaa) the amino acid sequences of both of SEQ ID NOs: 233 and 234; (bbbbbbb) the amino acid sequences of both of SEQ ID NOs: 235 and 236; (ccccccc) the amino acid sequence of SEQ ID NO: 237 (α chain of 4400 TCR-20 with N-terminal signal peptide), wherein: (i) X at position 184 of SEQ ID NO: 237 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 237 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 237 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 237 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ddddddd) the amino acid sequence of SEQ ID NO: 238 (β chain of 4400 TCR-20 with N-terminal signal peptide), wherein X at position 189 of SEQ ID NO: 238 is Ser or Cys; (eeeeeee) the amino acid sequences of both of SEQ ID NOs: 237 and 238; (ffffff) the amino acid sequence of SEQ ID NO: 239 (predicted sequence of α chain of 4400 TCR-20 without N-terminal signal peptide), wherein: (i) X at position 163 of SEQ ID NO: 239 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 239 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 239 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ggggggg) the amino acid sequence of SEQ ID NO: 240 (predicted sequence of β chain of 4400 TCR-20 without N-terminal signal peptide), wherein X at position 170 of SEQ ID NO: 240 is Ser or Cys; (hhhhhhh) the amino acid sequences of both of SEQ ID NOs: 239 and 240; (iiiiiii) the amino acid sequence of SEQ ID NO: 241 (α chain of cysteine-substituted, LVL-modified 4400 TCR-20 with N-terminal signal peptide); (jjjjjjj) the amino acid sequence of SEQ ID NO: 242 (β chain of cysteine-substituted, LVL-modified 4400 TCR-20 with N-terminal signal peptide); (kkkkkkk) the amino acid sequence of SEQ ID NO: 243 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-20 without N-terminal signal peptide); (lllllll) the amino acid sequence of SEQ ID NO: 244 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-20 without N-terminal signal peptide); (mmmmmmm) the amino acid sequences of both of SEQ ID NOs: 241 and 242; or (nnnnnnn) the amino acid sequences of both of SEQ ID NOs: 243 and 244.

[0073] 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 may be a cysteine-substituted TCR in which one or both of the native Thr at position 48 (Thr48) of SEQ ID NO: 63 and the native Ser at position 57 (Ser57) of SEQ ID NO: 64 may be substituted with Cys. Preferably, both of the native Thr48 of SEQ ID NO: 63 and the native Ser57 of SEQ ID NO: 64 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: 59, (ii) SEQ ID NO: 60, or (iii) both of SEQ ID NOs: 59 and 60, wherein both of SEQ ID NOs: 59 and 60 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.

[0074] 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: (1) SEQ ID NO: 59, (2) SEQ ID NO: 60, (3) SEQ ID NO: 65, (4) SEQ ID NO: 66, (5) SEQ ID NO: 67, (6) SEQ ID NO: 68, (7) SEQ ID NO: 73, (8) SEQ ID NO: 74, (9) SEQ ID NO: 75, (10) SEQ ID NO: 76, (11) SEQ ID NO: 81, (12) SEQ ID NO: 82, (13) SEQ ID NO: 83, (14) SEQ ID NO: 84, (15) SEQ ID NO: 89, (16) SEQ ID NO: 90, (17) SEQ ID NO: 91, (18) SEQ ID NO: 92, (19) SEQ ID NO: 97, (20) SEQ ID NO: 98, (21) SEQ ID NO: 99, (22) SEQ ID NO: 100, (23) SEQ ID NO: 189, (24) SEQ ID NO: 190, (25) SEQ ID NO: 191, (26) SEQ ID NO: 192, (27) SEQ ID NO: 197, (28) SEQ ID NO: 198, (29) SEQ ID NO: 199, (30) SEQ ID NO: 200, (31) SEQ ID NO: 205, (32) SEQ ID NO: 206, (33) SEQ ID NO: 207, (34) SEQ ID NO: 208, (35) SEQ ID NO: 213, (36) SEQ ID NO: 214, (37) SEQ ID NO: 215, (38) SEQ ID NO: 216, (39) SEQ ID NO: 221, (40) SEQ ID NO: 222, (41) SEQ ID NO: 223, (42) SEQ ID NO: 224, (43) SEQ ID NO: 229, (44) SEQ ID NO: 230, (45) SEQ ID NO: 231, (46) SEQ ID NO: 232, (47) SEQ ID NO: 237, (48) SEQ ID NO: 238, (49) SEQ ID NO: 239, (50) SEQ ID NO: 240, (51) both of SEQ ID NOs: 59 and 60, (52) both of SEQ ID NOs: 65 and 66, (53) both of SEQ ID NOs: 67 and 68, (54) both of SEQ ID NOs: 73 and 74, (55) both of SEQ ID NOs: 75 and 76, (56) both of SEQ ID NOs: 81 and 82,

(57) both of SEQ ID NOs: 83 and 84, (58) both of SEQ ID NOs: 89 and 90, (59) both of SEQ ID NOs: 91 and 92, (60) both of SEQ ID NOs: 97 and 98, (61) both of SEQ ID NOs: 99 and 100, (62) both of SEQ ID NOs: 189 and 190, (63) both of SEQ ID NOs: 191 and 192, (64) both of SEQ ID NOs: 197 and 198, (65) both of SEQ ID NOs: 199 and 200, (66) both of SEQ ID NOs: 205 and 206, (67) both of SEQ ID NOs: 207 and 208, (68) both of SEQ ID NOs: 213 and 214, (69) both of SEQ ID NOs: 215 and 216, (70) both of SEQ ID NOs: 221 and 222, (71) both of SEQ ID NOs: 223 and 224, (72) both of SEQ ID NOs: 229 and 230, (73) both of SEQ ID NOs: 231 and 232, (74) both of SEQ ID NOs: 237 and 238, or (75) both of SEQ ID NOs: 239 and 240, wherein all of SEQ ID NOs: 59-60, 65-68, 73-76, 81-84, 89-92, 97-100, 189-192, 197-200, 205-208, 213-216, 221-224, 229-232, and 237-240 are as defined in Table 2.

TABLE 2

SEQ ID NO:	Definitions of "X"
SEQ ID NO: 59 (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: 60 (constant region β chain)	X at position 57 is Cys
SEQ ID NO: 65 (4400 TCRA1 α chain with N-terminal signal peptide)	X at position 180 is Cys, X at position 244 is Ser, X at position 246 is Met, and X at position 247 is Gly.
SEQ ID NO: 66 (4400 TCR-A1 β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 67 (4400 TCR-A1 α chain predicted sequence without N-terminal signal peptide)	X at position 158 is Cys, X at position 222 is Ser, X at position 224 is Met, and X at position 225 is Gly.
SEQ ID NO: 68 (4400 TCR-A1 β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 73 (4400 TCR-A2 α chain with N-terminal signal peptide)	X at position 180 is Cys, X at position 244 is Ser, X at position 246 is Met, and

SEQ ID NO:	Definitions of "X"
	X at position 247 is Gly.
SEQ ID NO: 74 (4400 TCR-A2 β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 75 (4400 TCR-A2 α chain predicted sequence without N-terminal signal peptide)	X at position 158 is Cys, X at position 222 is Ser, X at position 224 is Met, and X at position 225 is Gly.
SEQ ID NO: 76 (4400 TCR-A2 β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 81 (4400 TCR-E α chain with N-terminal signal peptide)	X at position 177 is Cys, X at position 241 is Ser, X at position 243 is Met, and X at position 244 is Gly.
SEQ ID NO: 82 (4400 TCR-E β chain with N-terminal signal peptide)	X at position 189 is Cys
SEQ ID NO: 83 (4400 TCR-E α chain predicted sequence without N-terminal signal peptide)	X at position 160 is Cys, X at position 224 is Ser, X at position 226 is Met, and X at position 227 is Gly.
SEQ ID NO: 84 (4400 TCR-E β chain predicted sequence without N-terminal signal peptide)	X at position 170 is Cys
SEQ ID NO: 89 (4400 TCR-J α chain with N-terminal signal peptide)	X at position 183 is Cys, X at position 247 is Ser, X at position 249 is Met, and X at position 250 is Gly.
SEQ ID NO: 90 (4400 TCR-J β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 91 (4400 TCR-J α chain predicted sequence without N-terminal signal peptide)	X at position 161 is Cys, X at position 225 is Ser, X at position 227 is Met, and X at position 228 is Gly.
SEQ ID NO: 92 (4400 TCR-J β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 97	X at position 178 is Cys, X at position 242 is Ser,

SEQ ID NO:	Definitions of "X"
(4400 TCR-N α chain with N-terminal signal peptide)	X at position 244 is Met, and X at position 245 is Gly.
SEQ ID NO: 98 (4400 TCR-N β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 99 (4400 TCR-N α chain predicted sequence without N-terminal signal peptide)	X at position 157 is Cys, X at position 221 is Ser, X at position 223 is Met, and X at position 224 is Gly.
SEQ ID NO: 100 (4400 TCR-N β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 189 (α chain of 4400 TCR-A3 with N-terminal signal peptide)	X at position 176 is Cys; X at position 240 Ser; X at position 242 Met; and X at position 243 Gly.
SEQ ID NO: 190 (β chain of 4400 TCR-A3 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 191 (predicted sequence of α chain of 4400 TCR-A3 without N-terminal signal peptide)	X at position 157 is Cys; X at position 221 is Ser; X at position 223 is Met; and X at position 224 Gly.
SEQ ID NO: 192 (predicted sequence of β chain of 4400 TCR-A3 without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 197 (α chain of 4400 TCR-J2 with N-terminal signal peptide)	X at position 181 is Cys; X at position 245 is Ser; X at position 247 is Met; and X at position 248 is Gly.
SEQ ID NO: 198 (β chain of 4400 TCR-J2 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 199 (predicted sequence of α chain of 4400 TCR-J2 without N-terminal signal peptide)	X at position 161 is Cys; X at position 225 is Ser; X at position 227 is Met; and X at position 228 Gly.
SEQ ID NO: 200 (predicted sequence of β chain of 4400 TCR-J2 without N-terminal signal peptide)	X at position 169 is Cys

SEQ ID NO:	Definitions of "X"
SEQ ID NO: 205 (α chain of 4400 TCR-N4 with N-terminal signal peptide)	X at position 184 is Cys; X at position 248 is Ser; X at position 250 is Met; and X at position 251 is Gly.
SEQ ID NO: 206 (β chain of 4400 TCR-N4 with N-terminal signal peptide)	X at position 190 is Cys
SEQ ID NO: 207 (predicted sequence of α chain of 4400 TCR-N4 without N-terminal signal peptide)	X at position 163 is Cys; X at position 227 is Ser; X at position 229 is Met; and X at position 230 is Gly.
SEQ ID NO: 208 (predicted sequence of β chain of 4400 TCR-N4 without N-terminal signal peptide)	X at position 164 is Cys
SEQ ID NO: 213 (α chain of 4400 TCR-N12 with N-terminal signal peptide)	X at position 183 is Cys; X at position 247 is Ser; X at position 249 is Met; and X at position 250 is Gly.
SEQ ID NO: 214 (β chain of 4400 TCR-N12 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 215 (predicted sequence of α chain of 4400 TCR-N12 without N-terminal signal peptide)	X at position 161 is Cys; X at position 225 is Ser; X at position 227 is Met; and X at position 228 is Gly.
SEQ ID NO: 216 (predicted sequence of β chain of 4400 TCR-N12 without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 221 (α chain of 4400 TCR-N13 with N-terminal signal peptide)	X at position 180 is Cys; X at position 244 is Ser; X at position 246 is Met; and X at position 247 is Gly.
SEQ ID NO: 222 (β chain of 4400 TCR-N13 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 223 (predicted sequence of α chain of 4400 TCR-N13 without N-terminal signal peptide)	X at position 158 is Cys; X at position 222 is Ser; X at position 224 is Met; and X at position 225 is Gly.
SEQ ID NO: 224	X at position 169 is Cys

SEQ ID NO:	Definitions of "X"
(predicted sequence of β chain of 4400 TCR-N13 without N-terminal signal peptide)	
SEQ ID NO: 229 (α chain of 4400 TCR-C with N-terminal signal peptide)	X at position 184 is Cys; X at position 248 is Ser; X at position 250 is Met; and X at position 251 is Gly.
SEQ ID NO: 230 (β chain of 4400 TCR-C with N-terminal signal peptide)	X at position 189 is Cys
SEQ ID NO: 231 (predicted sequence of α chain of 4400 TCR-C without N-terminal signal peptide)	X at position 163 is Cys; X at position 227 is Ser; X at position 229 of is Met; and X at position 230 is Gly.
SEQ ID NO: 232 (predicted sequence of β chain of 4400 TCR-C without N-terminal signal peptide)	X at position 170 is Cys
SEQ ID NO: 237 (α chain of 4400 TCR-20 with N-terminal signal peptide)	X at position 184 is Cys; X at position 248 is Ser; X at position 250 is Met; and X at position 251 is Gly.
SEQ ID NO: 238 (β chain of 4400 TCR-20 with N-terminal signal peptide)	X at position 189 is Cys
SEQ ID NO: 239 (predicted sequence of α chain of 4400 TCR-20 without N-terminal signal peptide)	X at position 163 is Cys; X at position 227 is Ser; X at position 229 is Met; and X at position 230 is Gly.
SEQ ID NO: 240 (predicted sequence of β chain of 4400 TCR-20 without N-terminal signal peptide)	X at position 170 is Cys

[0075] 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: 63 may, independently, be substituted with Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably with Leu, Ile, or Val. Preferably, all three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 63 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: 59, (ii) SEQ ID NO: 60, or (iii) both of SEQ ID NOs: 59 and 60, wherein both of SEQ ID NOs: 59 and 60 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.

[0076] 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 TCR comprises: (1) SEQ ID NO: 59, (2) SEQ ID NO: 60, (3) SEQ ID NO: 65, (4) SEQ ID NO: 66, (5) SEQ ID NO: 67, (6) SEQ ID NO: 68, (7) SEQ ID NO: 73, (8) SEQ ID NO: 74, (9) SEQ ID NO: 75, (10) SEQ ID NO: 76, (11) SEQ ID NO: 81, (12) SEQ ID NO: 82, (13) SEQ ID NO: 83, (14) SEQ ID NO: 84, (15) SEQ ID NO: 89, (16) SEQ ID NO: 90, (17) SEQ ID NO: 91, (18) SEQ ID NO: 92, (19) SEQ ID NO: 97, (20) SEQ ID NO: 98, (21) SEQ ID NO: 99, (22) SEQ ID NO: 100, (23) SEQ ID NO: 189, (24) SEQ ID NO: 190, (25) SEQ ID NO: 191, (26) SEQ ID NO: 192, (27) SEQ ID NO: 197, (28) SEQ ID NO: 198, (29) SEQ ID NO: 199, (30) SEQ ID NO: 200, (31) SEQ ID NO: 205, (32) SEQ ID NO: 206, (33) SEQ ID NO: 207, (34) SEQ ID NO: 208, (35) SEQ ID NO: 213, (36) SEQ ID NO: 214, (37) SEQ ID NO: 215, (38) SEQ ID NO: 216, (39) SEQ ID NO: 221, (40) SEQ ID NO: 222, (41) SEQ ID NO: 223, (42) SEQ ID NO: 224, (43) SEQ ID NO: 229, (44) SEQ ID NO: 230, (45) SEQ ID NO: 231, (46) SEQ ID NO: 232, (47) SEQ ID NO: 237, (48) SEQ ID NO: 238, (49) SEQ ID NO: 239, (50) SEQ ID NO: 240, (51) both of SEQ ID NOs: 59 and 60, (52) both of SEQ ID NOs: 65 and 66, (53) both of SEQ ID NOs: 67 and 68, (54) both of SEQ ID NOs: 73 and 74, (55) both of SEQ ID NOs: 75 and 76, (56) both of SEQ ID NOs: 81 and 82, (57) both of SEQ ID NOs: 83 and 84, (58) both of SEQ ID NOs: 89 and 90, (59) both of SEQ ID NOs: 91 and 92, (60) both of SEQ ID NOs: 97 and 98, (61) both of SEQ ID NOs: 99 and 100, (62) both of SEQ ID NOs: 189 and 190, (63) both of SEQ ID NOs: 191 and 192, (64) both of SEQ ID NOs: 197 and 198, (65) both of SEQ ID NOs: 199 and 200, (66) both of SEQ ID NOs: 205 and 206, (67) both of SEQ ID NOs: 207 and 208, (68) both of SEQ ID NOs: 213 and 214, (69) both of SEQ ID NOs: 215 and 216, (70) both of SEQ ID NOs: 221 and 222, (71) both of

SEQ ID NOs: 223 and 224, (72) both of SEQ ID NOs: 229 and 230, (73) both of SEQ ID NOs: 231 and 232, (74) both of SEQ ID NOs: 237 and 238, or (75) both of SEQ ID NOs: 239 and 240, wherein all of SEQ ID NOs: 59-60, 65-68, 73-76, 81-84, 89-92, 97-100, 189-192, 197-200, 205-208, 213-216, 221-224, 229-232, and 237-240 are as defined in Table 3.

TABLE 3

SEQ ID NO:	Definitions of "X"
SEQ ID NO: 59 (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: 59 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 60 (constant region β chain)	X at position 57 is Ser
SEQ ID NO: 65 (4400 TCR-A1 α chain) (with N-terminal signal peptide)	X at position 180 is Thr; X at position 244 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Leu; X at position 246 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 246 is Leu, Ile, or Val; especially preferably wherein X at position 246 is Ile; and X at position 247 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Val, wherein SEQ ID NO: 65 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 66 (4400 TCR-A1 β chain) (with N-terminal signal peptide)	X at position 188 is Ser

SEQ ID NO:	Definitions of "X"
SEQ ID NO: 67 (4400 TCR-A1 α chain) (predicted sequence without N-terminal signal peptide)	X at position 158 is Thr; X at position 222 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 222 is Leu, Ile, or Val; especially preferably wherein X at position 222 is Leu; X at position 224 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Ile; and X at position 225 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Val, wherein SEQ ID NO: 67 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 68 (4400 TCR-A1 β chain) (predicted sequence without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 73 (4400 TCR-A2 α chain with N-terminal signal peptide)	X at position 180 is Thr; X at position 244 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Leu; X at position 246 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 246 is Leu, Ile, or Val; especially preferably wherein X at position 246 is Ile; and X at position 247 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Val, wherein SEQ ID NO: 73 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 74 (4400 TCR-A2 β chain with N-terminal signal peptide)	X at position 188 is Ser
SEQ ID NO: 75 (4400 TCR-A2 α chain predicted sequence without N-	X at position 158 is Thr; X at position 222 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 222 is Leu, Ile, or Val; especially preferably wherein X at position 222 is Leu; X at position 224 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp;

SEQ ID NO:	Definitions of "X"
terminal signal peptide)	preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Ile; and X at position 225 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Val, wherein SEQ ID NO: 75 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 76 (4400 TCR-A2 β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 81 (4400 TCR-E α chain with N-terminal signal peptide)	X at position 177 is Thr; X at position 241 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 241 is Leu, Ile, or Val; especially preferably wherein X at position 241 is Leu; X at position 243 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 243 is Leu, Ile, or Val; especially preferably wherein X at position 243 is Ile; and X at position 244 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Val, wherein SEQ ID NO: 81 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 82 (4400 TCR-E β chain with N-terminal signal peptide)	X at position 189 is Ser
SEQ ID NO: 83 (4400 TCR-E α chain predicted sequence without N-terminal signal peptide)	X at position 160 is Thr; X at position 224 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Leu; X at position 226 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 226 is Leu, Ile, or Val; especially preferably wherein X at position 226 is Ile; and X at position 227 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val;

SEQ ID NO:	Definitions of "X"
	especially preferably wherein X at position 227 is Val, wherein SEQ ID NO: 83 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 84 (4400 TCR-E β chain predicted sequence without N-terminal signal peptide)	X at position 170 is Ser
SEQ ID NO: 89 (4400 TCR-J α chain with N-terminal signal peptide)	X at position 183 is Thr; X at position 247 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Leu; X at position 249 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 249 is Leu, Ile, or Val; especially preferably wherein X at position 249 is Ile; and X at position 250 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Val, wherein SEQ ID NO: 89 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 90 (4400 TCR-J β chain with N-terminal signal peptide)	X at position 188 is Ser
SEQ ID NO: 91 (4400 TCR-J α chain predicted sequence without N-terminal signal peptide)	X at position 161 is Thr; X at position 225 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Leu; X at position 227 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Ile; and X at position 228 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 228 is Leu, Ile, or Val; especially preferably wherein X at position 228 is Val, wherein SEQ ID NO: 91 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 92	X at position 169 is Ser

SEQ ID NO:	Definitions of "X"
(4400 TCR-J β chain predicted sequence without N-terminal signal peptide)	
SEQ ID NO: 97 (4400 TCR-N α chain with N-terminal signal peptide)	X at position 178 is Thr; X at position 242 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 242 is Leu, Ile, or Val; especially preferably wherein X at position 242 is Leu; X at position 244 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Ile; and X at position 245 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 245 is Leu, Ile, or Val; especially preferably wherein X at position 245 is Val, wherein SEQ ID NO: 97 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 98 (4400 TCR-N β chain with N-terminal signal peptide)	X at position 188 is Ser
SEQ ID NO: 99 (4400 TCR-N α chain predicted sequence without N-terminal signal peptide)	X at position 157 is Thr; X at position 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 221 is Leu, Ile, or Val; especially preferably wherein X at position 221 is Leu; X at position 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 223 is Leu, Ile, or Val; especially preferably wherein X at position 223 is Ile; and X at position 224 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Val, wherein SEQ ID NO: 99 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 100 (4400 TCR-N β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 189	X at position 176 is Thr;

SEQ ID NO:	Definitions of "X"
(α chain of 4400 TCR-A3 with N-terminal signal peptide)	X at position 240 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 240 is Leu, Ile, or Val; especially preferably wherein X at position 240 is Leu; X at position 242 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 242 is Leu, Ile, or Val; especially preferably wherein X at position 242 is Ile; and X at position 243 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 243 is Leu, Ile, or Val; especially preferably wherein X at position 243 is Val, wherein SEQ ID NO: 189 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 190 (β chain of 4400 TCR-A3 with N-terminal signal peptide)	X at position 188 is Ser
SEQ ID NO: 191 (predicted sequence of α chain of 4400 TCR-A3 without N-terminal signal peptide)	X at position 157 is Thr; X at position 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 221 is Leu, Ile, or Val; especially preferably wherein X at position 221 is Leu; X at position 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 223 is Leu, Ile, or Val; especially preferably wherein X at position 223 is Ile; and X at position 224 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Val, wherein SEQ ID NO: 191 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 192 (predicted sequence of β chain of 4400 TCR-A3 without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 197 (α chain of 4400 TCR-J2 with N-	X at position 181 is Thr; X at position 245 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 245 is Leu, Ile, or Val; especially preferably wherein X at position 245 is Leu;

SEQ ID NO:	Definitions of "X"
terminal signal peptide)	X at position 247 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Ile; and X at position 248 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Val, wherein SEQ ID NO: 197 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 198 (β chain of 4400 TCR-J2 with N-terminal signal peptide)	X at position 188 is Ser
SEQ ID NO: 199 (predicted sequence of α chain of 4400 TCR-J2 without N-terminal signal peptide)	X at position 161 is Thr; X at position 225 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Leu; X at position 227 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Ile; and X at position 228 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 228 is Leu, Ile, or Val; especially preferably wherein X at position 228 is Val, wherein SEQ ID NO: 199 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 200 (predicted sequence of β chain of 4400 TCR-J2 without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 205 (α chain of 4400 TCR-N4 with N-terminal signal peptide)	X at position 184 is Thr; X at position 248 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Leu; X at position 250 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Ile; and

SEQ ID NO:	Definitions of "X"
	X at position 251 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 251 is Leu, Ile, or Val; especially preferably wherein X at position 251 is Val, wherein SEQ ID NO: 205 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 206 (β chain of 4400 TCR-N4 with N- terminal signal peptide)	X at position 190 is Ser
SEQ ID NO: 207 (predicted sequence of α chain of 4400 TCR-N4 without N- terminal signal peptide)	X at position 163 is Thr; X at position 227 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Leu; X at position 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Ile; and X at position 230 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 230 is Leu, Ile, or Val; especially preferably wherein X at position 230 is Val, wherein SEQ ID NO: 207 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 208 (predicted sequence of β chain of 4400 TCR-N4 without N- terminal signal peptide)	X at position 164 is Ser
SEQ ID NO: 213 (α chain of 4400 TCR-N12 with N- terminal signal peptide)	X at position 183 is Thr; X at position 247 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Leu; X at position 249 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 249 is Leu, Ile, or Val; especially preferably wherein X at position 249 is Ile; and X at position 250 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Val,

SEQ ID NO:	Definitions of "X"
	wherein SEQ ID NO: 213 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 214 (β chain of 4400 TCR-N12 with N-terminal signal peptide)	X at position 188 is Ser
SEQ ID NO: 215 (predicted sequence of α chain of 4400 TCR-N12 without N-terminal signal peptide)	X at position 161 is Thr; X at position 225 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Leu; X at position 227 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Ile; and X at position 228 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 228 is Leu, Ile, or Val; especially preferably wherein X at position 228 is Val, wherein SEQ ID NO: 215 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 216 (predicted sequence of β chain of 4400 TCR-N12 without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 221 (α chain of 4400 TCR-N13 with N-terminal signal peptide)	X at position 180 is Thr; X at position 244 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Leu; X at position 246 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 246 is Leu, Ile, or Val; especially preferably wherein X at position 246 is Ile; and X at position 247 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Val, wherein SEQ ID NO: 221 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 222	X at position 188 is Ser

SEQ ID NO:	Definitions of "X"
(β chain of 4400 TCR-N13 with N-terminal signal peptide)	
SEQ ID NO: 223 (predicted sequence of α chain of 4400 TCR-N13 without N-terminal signal peptide)	X at position 158 is Thr; X at position 222 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 222 is Leu, Ile, or Val; especially preferably wherein X at position 222 is Leu; X at position 224 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Ile; and X at position 225 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Val, wherein SEQ ID NO: 223 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 224 (predicted sequence of β chain of 4400 TCR-N13 without N-terminal signal peptide)	X at position 169 is Ser
SEQ ID NO: 229 (α chain of 4400 TCR-C with N-terminal signal peptide)	X at position 184 is Thr; X at position 248 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Leu; X at position 250 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Ile; and X at position 251 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 251 is Leu, Ile, or Val; especially preferably wherein X at position 251 is Val, wherein SEQ ID NO: 229 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 230 (β chain of 4400 TCR-C with N-	X at position 189 is Ser

SEQ ID NO:	Definitions of "X"
terminal signal peptide)	
SEQ ID NO: 231 (predicted sequence of α chain of 4400 TCR-C without N-terminal signal peptide)	X at position 163 is Thr; X at position 227 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Leu; X at position 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Ile; and X at position 230 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 230 is Leu, Ile, or Val; especially preferably wherein X at position 230 is Val, wherein SEQ ID NO: 231 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 232 (predicted sequence of β chain of 4400 TCR-C without N-terminal signal peptide)	X at position 170 is Ser
SEQ ID NO: 237 (α chain of 4400 TCR-20 with N-terminal signal peptide)	X at position 184 is Thr; X at position 248 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Leu; X at position 250 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Ile; and X at position 251 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 251 is Leu, Ile, or Val; especially preferably wherein X at position 251 is Val, wherein SEQ ID NO: 237 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 238 (β chain of 4400 TCR-20 with N-terminal signal peptide)	X at position 189 is Ser
SEQ ID NO: 239	X at position 163 is Thr;

SEQ ID NO:	Definitions of "X"
(predicted sequence of α chain of 4400 TCR-20 without N-terminal signal peptide)	X at position 227 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Leu; X at position 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Ile; and X at position 230 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 230 is Leu, Ile, or Val; especially preferably wherein X at position 230 is Val, wherein SEQ ID NO: 239 does not comprise SEQ ID NO: 63 (unsubstituted α chain constant region)
SEQ ID NO: 240 (predicted sequence of β chain of 4400 TCR-20 without N-terminal signal peptide)	X at position 170 is Ser

[0077] 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: 63 is substituted with Cys; one, two, or three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 63 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: 64 is substituted with Cys. Preferably, all three of the native Ser112, Met114, and Gly115 of SEQ ID NO: 63 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: 59, (ii) SEQ ID NO: 60, or (iii) both of SEQ ID NOs: 59 and 60, wherein both of SEQ ID NOs: 59 and 60 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.

[0078] In an embodiment, the cysteine-substituted, LVL-modified TCR comprises a full-length α chain and a full-length β chain. Examples of cysteine-substituted, LVL-modified TCR α chain and β chain sequences are set forth in Tables 4 and 7. In an embodiment of the invention, the TCR comprises: (1) SEQ ID NO: 59, (2) SEQ ID NO: 60, (3) SEQ ID NO: 65, (4) SEQ ID NO: 66, (5) SEQ ID NO: 67, (6) SEQ ID NO: 68, (7) SEQ ID NO: 69, (8) SEQ ID NO: 70, (9) SEQ ID NO: 71, (10) SEQ ID NO: 72, (11) SEQ ID NO: 73, (12) SEQ ID NO: 74, (13) SEQ ID NO: 75, (14) SEQ ID NO: 76, (15) SEQ ID NO: 77, (16) SEQ ID NO: 78, (17) SEQ ID NO: 79, (18) SEQ ID NO: 80, (19) SEQ ID NO: 81, (20) SEQ ID NO: 82, (21) SEQ ID NO: 83, (22) SEQ ID NO: 84, (23) SEQ ID NO: 85, (24) SEQ ID NO: 86, (25) SEQ ID NO: 87, (26) SEQ ID NO: 88, (27) SEQ ID NO: 89, (28) SEQ ID NO: 90, (29) SEQ ID NO: 91, (30) SEQ ID NO: 92, (31) SEQ ID NO: 93, (32) SEQ ID NO: 94, (33) SEQ ID NO: 95, (34) SEQ ID NO: 96, (35) SEQ ID NO: 97, (36) SEQ ID NO: 98, (37) SEQ ID NO: 99, (38) SEQ ID NO: 100, (39) SEQ ID NO: 101, (40) SEQ ID NO: 102, (41) SEQ ID NO: 103, (42) SEQ ID NO: 104, (43) SEQ ID NO: 189, (44) SEQ ID NO: 190, (45) SEQ ID NO: 191, (46) SEQ ID NO: 192, (47) SEQ ID NO: 193, (48) SEQ ID NO: 194, (49) SEQ ID NO: 195, (50) SEQ ID NO: 196, (51) SEQ ID NO: 197, (52) SEQ ID NO: 198, (53) SEQ ID NO: 199, (54) SEQ ID NO: 200, (55) SEQ ID NO: 201, (56) SEQ ID NO: 202, (57) SEQ ID NO: 203, (58) SEQ ID NO: 204, (59) SEQ ID NO: 205, (60) SEQ ID NO: 206, (61) SEQ ID NO: 207, (62) SEQ ID NO: 208, (63) SEQ ID NO: 209, (64) SEQ ID NO: 210, (65) SEQ ID NO: 211, (66) SEQ ID NO: 212, (67) SEQ ID NO: 213, (68) SEQ ID NO: 214, (69) SEQ ID NO: 215, (70) SEQ ID NO: 216, (71) SEQ ID NO: 217, (72) SEQ ID NO: 218, (73) SEQ ID NO: 219, (74) SEQ ID NO: 220, (75) SEQ ID NO: 221, (76) SEQ ID NO: 222, (77) SEQ ID NO: 223, (78) SEQ ID NO: 224, (79) SEQ ID NO: 225, (80) SEQ ID NO: 226, (81) SEQ ID NO: 227, (82) SEQ ID NO: 228, (83) SEQ ID NO: 229, (84) SEQ ID NO: 230, (85) SEQ ID NO: 231, (86) SEQ ID NO: 232, (87) SEQ ID NO: 233, (88) SEQ ID NO: 234, (89) SEQ ID NO: 235, (90) SEQ ID NO: 236, (91) SEQ ID NO: 237, (92) SEQ ID NO: 238, (93) SEQ ID NO: 239, (94) SEQ ID NO: 240, (95) SEQ ID NO: 241, (96) SEQ ID NO: 242, (97) SEQ ID NO: 243, (98) SEQ ID NO: 244, (99) both of SEQ ID NOs: 59 and 60, (100) both of SEQ ID NOs: 65 and 66, (101) both of SEQ ID NOs: 67 and 68, (102) both of SEQ ID NOs: 69 and 70, (103) both of SEQ ID NOs: 71 and 72, (104) both of SEQ ID NOs: 73 and 74, (105) both of SEQ ID NOs: 75 and 76, (106) both of SEQ ID NOs: 77 and 78, (107) both of SEQ ID NOs: 79 and 80, (108) both of SEQ ID NOs: 81 and 82, (109) both of SEQ ID NOs: 83 and 84, (110) both of SEQ ID NOs: 85 and 86, (111) both of SEQ ID NOs: 87 and 88, (112) both

of SEQ ID NOs: 89 and 90, (113) both of SEQ ID NOs: 91 and 92, (114) both of SEQ ID NOs: 93 and 94, (115) both of SEQ ID NOs: 95 and 96, (116) both of SEQ ID NOs: 97 and 98, (117) both of SEQ ID NOs: 99 and 100, (118) both of SEQ ID NOs: 101 and 102, (119) both of SEQ ID NOs: 103 and 104, (120) both of SEQ ID NOs: 189 and 190, (121) both of SEQ ID NOs: 191 and 192, (122) both of SEQ ID NOs: 193 and 194, (123) both of SEQ ID NOs: 195 and 196, (124) both of SEQ ID NOs: 197 and 198, (125) both of SEQ ID NOs: 199 and 200, (126) both of SEQ ID NOs: 201 and 202, (127) both of SEQ ID NOs: 203 and 204, (128) both of SEQ ID NOs: 205 and 206, (129) both of SEQ ID NOs: 207 and 208, (130) both of SEQ ID NOs: 209 and 210, (131) both of SEQ ID NOs: 211 and 212, (132) both of SEQ ID NOs: 213 and 214, (133) both of SEQ ID NOs: 215 and 216, (134) both of SEQ ID NOs: 217 and 218, (135) both of SEQ ID NOs: 219 and 220, (136) both of SEQ ID NOs: 221 and 222, (137) both of SEQ ID NOs: 223 and 224, (138) both of SEQ ID NOs: 225 and 226, (139) both of SEQ ID NOs: 227 and 228, (140) both of SEQ ID NOs: 229 and 230, (141) both of SEQ ID NOs: 231 and 232, (142) both of SEQ ID NOs: 233 and 234, (143) both of SEQ ID NOs: 235 and 236, (144) both of SEQ ID NOs: 237 and 238, (145) both of SEQ ID NOs: 239 and 240, (146) both of SEQ ID NOs: 241 and 242, or (147) both of SEQ ID NOs: 243 and 244, wherein all of SEQ ID NOs: 59-60, 65-68, 73-76, 81-84, 89-92, 97-100, 189-192, 197-200, 205-208, 213-216, 221-224, 229-232, and 237-240 are as defined in Table 4.

TABLE 4

SEQ ID NO:	Definitions of "X"
SEQ ID NO: 59 (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: 49 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"
SEQ ID NO: 60 (constant region β chain)	X at position 57 is Cys
SEQ ID NO: 65 (4400 TCR-A1 α chain) (with N-terminal signal peptide)	X at position 180 is Cys; X at position 244 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Leu; X at position 246 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 246 is Leu, Ile, or Val; especially preferably wherein X at position 246 is Ile; and X at position 247 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; and especially preferably wherein X at position 247 is Val, wherein SEQ ID NO: 65 does not simultaneously comprise all of Ser at position 244, Met at position 246, and Gly at position 247.
SEQ ID NO: 66 (4400 TCR-A1 β chain) (with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 67 (4400 TCR-A1 α chain) (predicted sequence without N-terminal signal peptide)	X at position 158 is Cys; X at position 222 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 222 is Leu, Ile, or Val; especially preferably wherein X at position 222 is Leu; X at position 224 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Ile; and X at position 225 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; and especially preferably wherein X at position 225 is Val, wherein SEQ ID NO: 67 does not simultaneously comprise all of Ser at position 222, Met at position 224, and Gly at position 225.
SEQ ID NO: 68 (4400 TCR-A1 β chain) (predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 73	X at position 180 is Cys; X at position 244 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

SEQ ID NO:	Definitions of "X"
(4400 TCR-A2 α chain with N-terminal signal peptide)	preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Leu; X at position 246 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 246 is Leu, Ile, or Val; especially preferably wherein X at position 246 is Ile; and X at position 247 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; and especially preferably wherein X at position 247 is Val, wherein SEQ ID NO: 73 does not simultaneously comprise all of Ser at position 244, Met at position 246, and Gly at position 247.
SEQ ID NO: 74 (4400 TCR-A2 β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 75 (4400 TCR-A2 α chain predicted sequence without N-terminal signal peptide)	X at position 158 is Cys; X at position 222 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 222 is Leu, Ile, or Val; especially preferably wherein X at position 222 is Leu; X at position 224 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Ile; and X at position 225 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; and especially preferably wherein X at position 225 is Val, wherein SEQ ID NO: 75 does not simultaneously comprise all of Ser at position 222, Met at position 224, and Gly at position 225.
SEQ ID NO: 76 (4400 TCR-A2 β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 81 (4400 TCR-E α chain with N-terminal signal peptide)	X at position 177 is Cys; X at position 241 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 241 is Leu, Ile, or Val; especially preferably wherein X at position 241 is Leu; X at position 243 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 243 is Leu, Ile, or Val; especially preferably wherein X at position 243 is Ile; and

SEQ ID NO:	Definitions of "X"
	X at position 244 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; and especially preferably wherein X at position 244 is Val, wherein SEQ ID NO: 81 does not simultaneously comprise all of Ser at position 241, Met at position 243, and Gly at position 244.
SEQ ID NO: 82 (4400 TCR-E β chain with N-terminal signal peptide)	X at position 189 is Cys
SEQ ID NO: 83 (4400 TCR-E α chain predicted sequence without N-terminal signal peptide)	X at position 160 is Cys; X at position 224 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Leu; X at position 226 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 226 is Leu, Ile, or Val; especially preferably wherein X at position 226 is Ile; and X at position 227 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; and especially preferably wherein X at position 227 is Val, wherein SEQ ID NO: 83 does not simultaneously comprise all of Ser at position 224, Met at position 226, and Gly at position 227.
SEQ ID NO: 84 (4400 TCR-E β chain predicted sequence without N-terminal signal peptide)	X at position 170 is Cys
SEQ ID NO: 89 (4400 TCR-J α chain with N-terminal signal peptide)	X at position 183 is Cys; X at position 247 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Leu; X at position 249 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 249 is Leu, Ile, or Val; especially preferably wherein X at position 249 is Ile; and X at position 250 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; and especially preferably wherein X at position 250 is Val, wherein SEQ ID NO: 89 does not simultaneously comprise all of Ser at position 247, Met at position 249, and Gly at position 250.

SEQ ID NO:	Definitions of "X"
SEQ ID NO: 90 (4400 TCR-J β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 91 (4400 TCR-J α chain predicted sequence without N-terminal signal peptide)	X at position 161 is Cys; X at position 225 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Leu; X at position 227 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Ile; and X at position 228 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 228 is Leu, Ile, or Val; and especially preferably wherein X at position 228 is Val, wherein SEQ ID NO: 91 does not simultaneously comprise all of Ser at position 225, Met at position 227, and Gly at position 228.
SEQ ID NO: 92 (4400 TCR-J β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 97 (4400 TCR-N α chain with N-terminal signal peptide)	X at position 178 is Cys; X at position 242 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 242 is Leu, Ile, or Val; especially preferably wherein X at position 242 is Leu; X at position 244 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val; especially preferably wherein X at position 244 is Ile; and X at position 245 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 245 is Leu, Ile, or Val; and especially preferably wherein X at position 245 is Val, wherein SEQ ID NO: 97 does not simultaneously comprise all of Ser at position 242, Met at position 244, and Gly at position 245.
SEQ ID NO: 98 (4400 TCR-N β chain with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 99	X at position 157 is Cys;

SEQ ID NO:	Definitions of "X"
(4400 TCR-N α chain predicted sequence without N-terminal signal peptide)	X at position 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 221 is Leu, Ile, or Val; especially preferably wherein X at position 221 is Leu; X at position 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 223 is Leu, Ile, or Val; especially preferably wherein X at position 223 is Ile; and X at position 224 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; and especially preferably wherein X at position 224 is Val, wherein SEQ ID NO: 99 does not simultaneously comprise all of Ser at position 221, Met at position 223, and Gly at position 224.
SEQ ID NO: 100 (4400 TCR-N β chain predicted sequence without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 189 (α chain of 4400 TCR-A3 with N-terminal signal peptide)	X at position 176 is Cys; X at position 240 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 240 is Leu, Ile, or Val; especially preferably wherein X at position 240 is Leu; X at position 242 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 242 is Leu, Ile, or Val; especially preferably wherein X at position 242 is Ile; and X at position 243 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 243 is Leu, Ile, or Val; and especially preferably wherein X at position 243 is Val, wherein SEQ ID NO: 189 does not simultaneously comprise all of Ser at position 240, Met at position 242, and Gly at position 243.
SEQ ID NO: 190 (β chain of 4400 TCR-A3 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 191 (predicted sequence of α chain of 4400 TCR-A3 without N-terminal signal peptide)	X at position 157 is Cys; X at position 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 221 is Leu, Ile, or Val; especially preferably wherein X at position 221 is Leu; X at position 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 223 is Leu, Ile, or Val;

SEQ ID NO:	Definitions of "X"
	especially preferably wherein X at position 223 is Ile; and X at position 224 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; and especially preferably wherein X at position 224 is Val, wherein SEQ ID NO: 191 does not simultaneously comprise all of Ser at position 221, Met at position 223, and Gly at position 224.
SEQ ID NO: 192 (predicted sequence of β chain of 4400 TCR-A3 without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 197 (α chain of 4400 TCR- J2 with N-terminal signal peptide)	X at position 181 is Cys; X at position 245 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 245 is Leu, Ile, or Val; especially preferably wherein X at position 245 is Leu; X at position 247 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Ile; and X at position 248 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; and especially preferably wherein X at position 248 is Val, wherein SEQ ID NO: 197 does not simultaneously comprise all of Ser at position 245, Met at position 247, and Gly at position 248.
SEQ ID NO: 198 (β chain of 4400 TCR- J2 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 199 (predicted sequence of α chain of 4400 TCR-J2 without N-terminal signal peptide)	X at position 16180 is Cys; X at position 225 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Leu; X at position 227 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Ile; and X at position 228 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 228 is Leu, Ile, or Val; and especially preferably wherein X at position 228 is Val,

SEQ ID NO:	Definitions of "X"
	wherein SEQ ID NO: 199 does not simultaneously comprise all of Ser at position 225, Met at position 227, and Gly at position 228.
SEQ ID NO: 200 (predicted sequence of β chain of 4400 TCR-J2 without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 205 (α chain of 4400 TCR-N4 with N-terminal signal peptide)	X at position 184 is Cys; X at position 248 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Leu; X at position 250 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Ile; and X at position 251 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 251 is Leu, Ile, or Val; and especially preferably wherein X at position 251 is Val, wherein SEQ ID NO: 205 does not simultaneously comprise all of Ser at position 248, Met at position 250, and Gly at position 251.
SEQ ID NO: 206 (β chain of 4400 TCR-N4 with N-terminal signal peptide)	X at position 190 is Cys;
SEQ ID NO: 207 (predicted sequence of α chain of 4400 TCR-N4 without N-terminal signal peptide)	X at position 163 is Cys; X at position 227 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Leu; X at position 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Ile; and X at position 230 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 230 is Leu, Ile, or Val; and especially preferably wherein X at position 230 is Val, wherein SEQ ID NO: 207 does not simultaneously comprise all of Ser at position 227, Met at position 229, and Gly at position 230.
SEQ ID NO: 208 (predicted sequence of β chain of 4400 TCR-	X at position 164 is Cys

SEQ ID NO:	Definitions of "X"
N4 without N-terminal signal peptide)	
SEQ ID NO: 213 (α chain of 4400 TCR-N12 with N-terminal signal peptide)	X at position 183 is Cys; X at position 247 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; especially preferably wherein X at position 247 is Leu; X at position 249 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 249 is Leu, Ile, or Val; especially preferably wherein X at position 249 is Ile; and X at position 250 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; and especially preferably wherein X at position 250 is Val, wherein SEQ ID NO: 213 does not simultaneously comprise all of Ser at position 247, Met at position 249, and Gly at position 250.
SEQ ID NO: 214 (β chain of 4400 TCR-N12 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 215 (predicted sequence of α chain of 4400 TCR-N12 without N-terminal signal peptide)	X at position 161 is Cys; X at position 225 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; especially preferably wherein X at position 225 is Leu; X at position 227 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Ile; and X at position 228 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 228 is Leu, Ile, or Val; and especially preferably wherein X at position 228 is Val, wherein SEQ ID NO: 215 does not simultaneously comprise all of Ser at position 225, Met at position 227, and Gly at position 228.
SEQ ID NO: 216 (predicted sequence of β chain of 4400 TCR-N12 without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 221	X at position 180 is Cys; X at position 244 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 244 is Leu, Ile, or Val;

SEQ ID NO:	Definitions of "X"
(α chain of 4400 TCR-N13 with N-terminal signal peptide)	especially preferably wherein X at position 244 is Leu; X at position 246 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 246 is Leu, Ile, or Val; especially preferably wherein X at position 246 is Ile; and X at position 247 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 247 is Leu, Ile, or Val; and especially preferably wherein X at position 247 is Val, wherein SEQ ID NO: 221 does not simultaneously comprise all of Ser at position 244, Met at position 246, and Gly at position 247.
SEQ ID NO: 222 (β chain of 4400 TCR-N13 with N-terminal signal peptide)	X at position 188 is Cys
SEQ ID NO: 223 (predicted sequence of α chain of 4400 TCR-N13 without N-terminal signal peptide)	X at position 158 is Cys; X at position 222 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 222 is Leu, Ile, or Val; especially preferably wherein X at position 222 is Leu; X at position 224 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 224 is Leu, Ile, or Val; especially preferably wherein X at position 224 is Ile; and X at position 225 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 225 is Leu, Ile, or Val; and especially preferably wherein X at position 225 is Val, wherein SEQ ID NO: 223 does not simultaneously comprise all of Ser at position 222, Met at position 224, and Gly at position 225.
SEQ ID NO: 224 (predicted sequence of β chain of 4400 TCR-N13 without N-terminal signal peptide)	X at position 169 is Cys
SEQ ID NO: 229 (α chain of 4400 TCR-C with N-terminal signal peptide)	X at position 184 is Cys; X at position 248 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Leu; X at position 250 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Ile; and X at position 251 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

SEQ ID NO:	Definitions of "X"
	preferably wherein X at position 251 is Leu, Ile, or Val; and especially preferably wherein X at position 251 is Val, wherein SEQ ID NO: 229 does not simultaneously comprise all of Ser at position 248, Met at position 250, and Gly at position 251.
SEQ ID NO: 230 (β chain of 4400 TCR-C with N-terminal signal peptide)	X at position 189 is Cys
SEQ ID NO: 231 (predicted sequence of α chain of 4400 TCR-C without N-terminal signal peptide)	X at position 163 is Cys; X at position 227 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Leu; X at position 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Ile; and X at position 230 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 230 is Leu, Ile, or Val; and especially preferably wherein X at position 230 is Val, wherein SEQ ID NO: 231 does not simultaneously comprise all of Ser at position 227, Met at position 229, and Gly at position 230.
SEQ ID NO: 232 (predicted sequence of β chain of 4400 TCR-C without N-terminal signal peptide)	X at position 170 is Cys
SEQ ID NO: 237 (α chain of 4400 TCR-20 with N-terminal signal peptide)	X at position 184 is Cys; X at position 248 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 248 is Leu, Ile, or Val; especially preferably wherein X at position 248 is Leu; X at position 250 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 250 is Leu, Ile, or Val; especially preferably wherein X at position 250 is Ile; and X at position 251 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 251 is Leu, Ile, or Val; and especially preferably wherein X at position 251 is Val, wherein SEQ ID NO: 237 does not simultaneously comprise all of Ser at position 248, Met at position 250, and Gly at position 251.
SEQ ID NO: 238	X at position 189 is Cys

SEQ ID NO:	Definitions of "X"
(β chain of 4400 TCR-20 with N-terminal signal peptide)	
SEQ ID NO: 239 (predicted sequence of α chain of 4400 TCR-20 without N-terminal signal peptide)	X at position 163 is Cys; X at position 227 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 227 is Leu, Ile, or Val; especially preferably wherein X at position 227 is Leu; X at position 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; preferably wherein X at position 229 is Leu, Ile, or Val; especially preferably wherein X at position 229 is Ile; and X at position 230 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; preferably wherein X at position 230 is Leu, Ile, or Val; and especially preferably wherein X at position 230 is Val, wherein SEQ ID NO: 239 does not simultaneously comprise all of Ser at position 227, Met at position 229, and Gly at position 230.
SEQ ID NO: 240 (predicted sequence of β chain of 4400 TCR-20 without N-terminal signal peptide)	X at position 170 is Cys

[0079] In an embodiment of the invention, the cysteine-substituted, LVL-modified TCR comprises (a) SEQ ID NO: 61 (α chain constant region of cysteine-substituted, LVL-modified TCR); (b) SEQ ID NO: 62 (β chain constant region of cysteine-substituted, LVL-modified TCR); or (c) both (a) and (b).

[0080] 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.

[0081] 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 G13D 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 G13D RAS (e.g., within the context of any of the HLA Class II molecules described herein), 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 70%, about 80%, about 90%, about 95%, or more, of the parent TCR.

[0082] 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 G13D 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.

[0083] 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 of 4400 TCR-A1), SEQ ID NO: 2 (CDR2 of α chain of 4400 TCR-A1), SEQ ID NO: 3 (CDR3 of α chain of 4400 TCR-A1), SEQ ID NO: 4 (CDR1 of β chain of 4400 TCR-A1), SEQ ID NO: 5 (CDR2 of β chain of 4400 TCR-A1), SEQ ID NO: 6 (CDR3 of β chain of 4400 TCR-A1), SEQ ID NO: 11 (CDR1 of α chain of 4400 TCR-A2), SEQ ID NO: 12 (CDR2 of α chain of 4400 TCR-A2), SEQ ID NO: 13 (CDR3 of α chain of 4400 TCR-A2), SEQ ID NO: 14 (CDR1 of β chain of 4400 TCR-A2), SEQ ID NO: 15 (CDR2 of β chain of 4400 TCR-A2), SEQ ID NO: 16 (CDR3 of β chain of 4400 TCR-A2), SEQ ID NO: 21 (CDR1 of α chain of 4400 TCR-E), SEQ ID NO: 22 (CDR2 of α chain of 4400 TCR-E), SEQ ID NO: 23 (CDR3 of α chain of 4400 TCR-E), SEQ ID NO: 24 (CDR1 of β chain of 4400 TCR-E), SEQ ID NO: 25 (CDR2 of β chain of 4400 TCR-E), SEQ ID NO: 26 (CDR3 of β chain of 4400 TCR-E), SEQ ID NO: 31 (CDR1 of α chain of 4400 TCR-J), SEQ ID NO: 32 (CDR2 of α chain of 4400 TCR-J), SEQ ID NO: 33 (CDR3 of α chain of 4400 TCR-J), SEQ ID NO: 34 (CDR1 of β chain of 4400 TCR-J), SEQ ID NO: 35 (CDR2 of β chain of 4400 TCR-J), SEQ ID NO: 36 (CDR3 of β chain of 4400 TCR-J), SEQ ID NO: 41 (CDR1 of α chain of 4400 TCR-N), SEQ ID NO: 42 (CDR2 of α chain of 4400 TCR-N), SEQ ID NO: 43 (CDR3 of α chain of 4400 TCR-N), SEQ ID NO: 44 (CDR1 of β chain of 4400 TCR-N), SEQ ID NO: 45 (CDR2 of β chain of 4400 TCR-N), SEQ ID

NO: 46 (CDR3 of β chain of 4400 TCR-N), SEQ ID NO: 119 (CDR1 of α chain of 4400 TCR-A3), SEQ ID NO: 120 (CDR2 of α chain of 4400 TCR-A3), SEQ ID NO: 121 (CDR3 of α chain of 4400 TCR-A3), SEQ ID NO: 122 (CDR1 of β chain of 4400 TCR-A3), SEQ ID NO: 123 (CDR2 of β chain of 4400 TCR-A3), SEQ ID NO: 124 (CDR3 of β chain of 4400 TCR-A3), SEQ ID NO: 129 (CDR1 of α chain of 4400 TCR-J2), SEQ ID NO: 130 (CDR2 of α chain of 4400 TCR-J2), SEQ ID NO: 131 (CDR3 of α chain of 4400 TCR-J2), SEQ ID NO: 132 (CDR1 of β chain of 4400 TCR-J2), SEQ ID NO: 133 (CDR2 of β chain of 4400 TCR-J2), SEQ ID NO: 134 (CDR3 of β chain of 4400 TCR-J2), SEQ ID NO: 139 (CDR1 of α chain of 4400 TCR-N4), SEQ ID NO: 140 (CDR2 of α chain of 4400 TCR-N4), SEQ ID NO: 141 (CDR3 of α chain of 4400 TCR-N4), SEQ ID NO: 142 (CDR1 of β chain of 4400 TCR-N4), SEQ ID NO: 143 (CDR2 of β chain of 4400 TCR-N4), SEQ ID NO: 144 (CDR3 of β chain of 4400 TCR-N4), SEQ ID NO: 149 (CDR1 of α chain of 4400 TCR-N12), SEQ ID NO: 150 (CDR2 of α chain of 4400 TCR-N12), SEQ ID NO: 151 (CDR3 of α chain of 4400 TCR-N12), SEQ ID NO: 152 (CDR1 of β chain of 4400 TCR-N12), SEQ ID NO: 153 (CDR2 of β chain of 4400 TCR-N12), SEQ ID NO: 154 (CDR3 of β chain of 4400 TCR-N12), SEQ ID NO: 159 (CDR1 of α chain of 4400 TCR-N13), SEQ ID NO: 160 (CDR2 of α chain of 4400 TCR-N13), SEQ ID NO: 161 (CDR3 of α chain of 4400 TCR-N13), SEQ ID NO: 162 (CDR1 of β chain of 4400 TCR-N13), SEQ ID NO: 163 (CDR2 of β chain of 4400 TCR-N13), SEQ ID NO: 164 (CDR3 of β chain of 4400 TCR-N13), SEQ ID NO: 169 (CDR1 of α chain of 4400 TCR-C), SEQ ID NO: 170 (CDR2 of α chain of 4400 TCR-C), SEQ ID NO: 171 (CDR3 of α chain of 4400 TCR-C), SEQ ID NO: 172 (CDR1 of β chain of 4400 TCR-C), SEQ ID NO: 173 (CDR2 of β chain of 4400 TCR-C), SEQ ID NO: 174 (CDR3 of β chain of 4400 TCR-C), SEQ ID NO: 179 (CDR1 of α chain of 4400 TCR-20), SEQ ID NO: 180 (CDR2 of α chain of 4400 TCR-20), SEQ ID NO: 181 (CDR3 of α chain of 4400 TCR-20), SEQ ID NO: 182 (CDR1 of β chain of 4400 TCR-20), SEQ ID NO: 183 (CDR2 of β chain of 4400 TCR-20), SEQ ID NO: 184 (CDR3 of β chain of 4400 TCR-20), or a combination thereof. In this regard, the inventive polypeptide can comprise any one or more of the amino acid sequences selected from the group consisting of SEQ ID NOs: 1-6, 11-16, 21-26, 31-36, 41-46, 119-124, 129-134, 139-144, 149-154, 159-164, 169-174, or 179-184. In an embodiment of the invention, the polypeptide comprises the amino acid sequences of: (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, (c) all of SEQ ID NOs: 1-6, (d) all of SEQ ID NOs: 11-13, (e) all of SEQ ID NOs: 14-16, (f) all of SEQ ID NOs: 11-16, (g) all of SEQ ID NOs: 21-23, (h) all of SEQ ID NOs: 24-26, (i) all of SEQ ID NOs: 21-26, (j) all of SEQ

ID NOs: 31-33, (k) all of SEQ ID NOs: 34-36, (l) all of SEQ ID NOs: 31-36, (m) all of SEQ ID NOs: 41-43, (n) all of SEQ ID NOs: 44-46, (o) all of SEQ ID NOs: 41-46, (p) all of SEQ ID NOs: 119-121, (q) all of SEQ ID NOs: 122-124, (r) all of SEQ ID NOs: 119-124, (s) all of SEQ ID NOs: 129-131, (t) all of SEQ ID NOs: 132-134, (u) all of SEQ ID NOs: 129-134, (v) all of SEQ ID NOs: 139-141, (w) all of SEQ ID NOs: 142-144, (x) all of SEQ ID NOs: 139-144, (y) all of SEQ ID NOs: 149-151, (z) all of SEQ ID NOs: 152-154, (aa) all of SEQ ID NOs: 149-154, (bb) all of SEQ ID NOs: 159-161, (cc) all of SEQ ID NOs: 162-164, (dd) all of SEQ ID NOs: 159-164, (ee) all of SEQ ID NOs: 169-171, (ff) all of SEQ ID NOs: 172-174, (gg) all of SEQ ID NOs: 169-174, (hh) all of SEQ ID NOs: 179-181, (ii) all of SEQ ID NOs: 182-184, or (jj) all of SEQ ID NOs: 179-184. In a preferred embodiment, the polypeptide comprises the amino acid sequences of all of (i) SEQ ID NOs: 1-6, (ii) SEQ ID NOs: 11-16, (iii) SEQ ID NOs: 21-26, (iv) SEQ ID NOs: 31-36, (v) SEQ ID NOs: 41-46, (vi) all of SEQ ID NOs: 119-124, (vii) all of SEQ ID NOs: 129-134, (viii) all of SEQ ID NOs: 139-144, (ix) all of SEQ ID NOs: 149-154, (x) all of SEQ ID NOs: 159-164, (xi) all of SEQ ID NOs: 169-174, or (xii) all of SEQ ID NOs: 179-184.

[0084] 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(s) of (1) SEQ ID NO: 7, (2) SEQ ID NO: 8, (3) SEQ ID NO: 9, (4) SEQ ID NO: 10, (5) SEQ ID NO: 17, (6) SEQ ID NO: 18, (7) SEQ ID NO: 19, (8) SEQ ID NO: 20, (9) SEQ ID NO: 27, (10) SEQ ID NO: 28, (11) SEQ ID NO: 29, (12) SEQ ID NO: 30, (13) SEQ ID NO: 37, (14) SEQ ID NO: 38, (15) SEQ ID NO: 39, (16) SEQ ID NO: 40, (17) SEQ ID NO: 47, (18) SEQ ID NO: 48, (19) SEQ ID NO: 49, (20) SEQ ID NO: 50, (21) SEQ ID NO: 125, (22) SEQ ID NO: 126, (23) SEQ ID NO: 127, (24) SEQ ID NO: 128, (25) SEQ ID NO: 135, (26) SEQ ID NO: 136, (27) SEQ ID NO: 137, (28) SEQ ID NO: 138, (29) SEQ ID NO: 145, (30) SEQ ID NO: 146, (31) SEQ ID NO: 147, (32) SEQ ID NO: 148, (33) SEQ ID NO: 155, (34) SEQ ID NO: 156, (35) SEQ ID NO: 157, (36) SEQ ID NO: 158, (37) SEQ ID NO: 165, (38) SEQ ID NO: 166, (39) SEQ ID NO: 167, (40) SEQ ID NO: 168, (41) SEQ ID NO: 175, (42) SEQ ID NO: 176, (43) SEQ ID NO: 177, (44) SEQ ID NO: 178, (45) SEQ ID NO: 185, (46) SEQ ID NO: 186, (47) SEQ ID NO: 187, (48) SEQ ID NO: 188, (49) both of SEQ ID NOs: 7 and 8, (50) both of SEQ ID NOs: 9 and 10, (51) both of SEQ ID NOs: 17 and 18, (52) both of SEQ ID NOs: 19 and 20, (53) both of SEQ ID NOs: 27 and 28, (54) both of SEQ ID NOs: 29 and 30, (55) both of SEQ ID NOs: 37 and 38, (56) both of SEQ ID NOs: 39 and

40, (57) both of SEQ ID NOs: 47 and 48, (58) both of SEQ ID NOs: 49 and 50, (59) both of SEQ ID NOs: 125 and 126, (60) both of SEQ ID NOs: 127 and 128, (61) both of SEQ ID NOs: 135 and 136, (62) both of SEQ ID NOs: 137 and 138, (63) both of SEQ ID NOs: 145 and 146, (64) both of SEQ ID NOs: 147 and 148, (65) both of SEQ ID NOs: 155 and 156, (66) both of SEQ ID NOs: 157 and 158, (67) both of SEQ ID NOs: 165 and 166, (68) both of SEQ ID NOs: 167 and 168, (69) both of SEQ ID NOs: 175 and 176, (70) both of SEQ ID NOs: 177 and 178, (71) both of SEQ ID NOs: 185 and 186, or (72) both of SEQ ID NOs: 187 and 188. In a preferred embodiment, the polypeptide comprises the amino acid sequences of (a) both of SEQ ID NOs: 7 and 8, (b) both of SEQ ID NOs: 9 and 10, (c) both of SEQ ID NOs: 17 and 18, (d) both of SEQ ID NOs: 19 and 20, (e) both of SEQ ID NOs: 27 and 28, (f) both of SEQ ID NOs: 29 and 30, (g) both of SEQ ID NOs: 37 and 38, (h) both of SEQ ID NOs: 39 and 40, (i) both of SEQ ID NOs: 47 and 48, (j) both of SEQ ID NOs: 49 and 50, (k) both of SEQ ID NOs: 125 and 126, (l) both of SEQ ID NOs: 127 and 128, (m) both of SEQ ID NOs: 135 and 136, (n) both of SEQ ID NOs: 137 and 138, (o) both of SEQ ID NOs: 145 and 146, (p) both of SEQ ID NOs: 147 and 148, (q) both of SEQ ID NOs: 155 and 156, (r) both of SEQ ID NOs: 157 and 158, (s) both of SEQ ID NOs: 165 and 166, (t) both of SEQ ID NOs: 167 and 168, (u) both of SEQ ID NOs: 175 and 176, (v) both of SEQ ID NOs: 177 and 178, (w) both of SEQ ID NOs: 185 and 186, or (x) both of SEQ ID NOs: 187 and 188.

[0085] 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: 63 (WT murine constant region of α chain), SEQ ID NO: 64 (WT murine constant region of β chain), SEQ ID NO: 59 (substituted murine constant region of α chain), SEQ ID NO: 60 (substituted murine constant region of β chain), SEQ ID NO: 61 (α chain constant region of cysteine-substituted, LVL-modified TCR); SEQ ID NO: 62 (β chain constant region of cysteine-substituted, LVL-modified TCR); both SEQ ID NOs: 59 and 60, both SEQ ID NOs: 61 and 62, or both SEQ ID NOs: 63 and 64. Preferably, the polypeptide further comprises the amino acid sequences of both of SEQ ID NOs: 59 and 60, both of SEQ ID NO: 61 and 62, or both of SEQ ID NOs: 63 and 64 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: 59 and 60 of the polypeptide are as defined in any one of Tables 2-4.

[0086] 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: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, or SEQ ID NO: 244.

[0087] Alternatively, the polypeptide of the invention can comprise both chains of the TCRs described herein. For example, the polypeptide may comprise the amino acid sequences of: both of SEQ ID NOs: 65-66, both of SEQ ID NOs: 67-68, both of SEQ ID NOs: 69-70, both of SEQ ID NOs: 71-72, both of SEQ ID NOs: 73-74, both of SEQ ID NOs: 75-76, both of SEQ ID NOs: 77-78, both of SEQ ID NOs: 79-80, both of SEQ ID NOs: 81-82, both of SEQ ID NOs: 83-84, both of SEQ ID NOs: 85-86, both of SEQ ID NOs: 87-88, both of SEQ ID NOs: 89-90, both of SEQ ID NOs: 91-92, both of SEQ ID NOs: 93-94, both of SEQ ID NOs: 95-96, both of SEQ ID NOs: 97-98, both of SEQ ID NOs: 99-100, both of SEQ ID NOs: 101-102, both of SEQ ID NOs: 103-104, both of SEQ ID NOs: 189 and 190, both of SEQ ID NOs: 191 and 192, both of SEQ ID NOs: 193 and 194, both of SEQ ID NOs: 195 and 196, both of SEQ ID NOs: 197 and 198, both of SEQ ID NOs: 199 and 200, both of SEQ ID NOs: 201 and 202, both of SEQ ID NOs: 203 and 204, both of SEQ ID NOs: 205 and 206, both of SEQ ID NOs: 207 and 208, both of SEQ ID NOs: 209 and 210, both of SEQ

ID NOs: 211 and 212, both of SEQ ID NOs: 213 and 214, both of SEQ ID NOs: 215 and 216, both of SEQ ID NOs: 217 and 218, both of SEQ ID NOs: 219 and 220, both of SEQ ID NOs: 221 and 222, both of SEQ ID NOs: 223 and 224, both of SEQ ID NOs: 225 and 226, both of SEQ ID NOs: 227 and 228, both of SEQ ID NOs: 229 and 230, both of SEQ ID NOs: 231 and 232, both of SEQ ID NOs: 233 and 234, both of SEQ ID NOs: 235 and 236, both of SEQ ID NOs: 237 and 238, both of SEQ ID NOs: 239 and 240, both of SEQ ID NOs: 241 and 242, or both of SEQ ID NOs: 243 and 244.

[0088] For example, the polypeptide of the invention can comprise (a) the amino acid sequence of SEQ ID NO: 65 (α chain of 4400 TCR-A1 with N-terminal signal peptide), wherein: (i) X at position 180 of SEQ ID NO: 65 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 65 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 65 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 65 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (b) the amino acid sequence of SEQ ID NO: 66 (β chain of 4400 TCR-A1 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 66 is Ser or Cys; (c) the amino acid sequences of both of SEQ ID NOs: 65 and 66; (d) the amino acid sequence of SEQ ID NO: 67 (predicted sequence of α chain of 4400 TCR-A1 without N-terminal signal peptide), wherein: (i) X at position 158 of SEQ ID NO: 67 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 67 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 67 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 67 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (e) the amino acid sequence of SEQ ID NO: 68 (predicted sequence of β chain of 4400 TCR-A1 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 68 is Ser or Cys; (f) the amino acid sequences of both of SEQ ID NOs: 67 and 68; (g) the amino acid sequence of SEQ ID NO: 69 (α chain of cysteine-substituted, LVL-modified 4400 TCR-A1 with N-terminal signal peptide); (h) the amino acid sequence of SEQ ID NO: 70 (β chain of cysteine-substituted, LVL-modified 4400 TCR-A1 with N-terminal signal peptide); (i) the amino acid sequence of SEQ ID NO: 71 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-A1 without N-terminal signal peptide); (j) the amino acid sequence of SEQ ID NO: 72 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-A1 without N-terminal signal peptide); (k) the amino acid sequences of both of SEQ ID NOs: 69 and 70; (l) the amino acid sequences of both of SEQ ID NOs: 71 and 72; (m) the amino acid sequence of SEQ ID NO: 73 (α chain of 4400 TCR-A2 with N-terminal signal peptide), wherein: (i) X at position 180 of SEQ ID NO: 73 is

Thr or Cys; (ii) X at position 244 of SEQ ID NO: 73 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 73 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 73 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (n) the amino acid sequence of SEQ ID NO: 74 (β chain of 4400 TCR-A2 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 74 is Ser or Cys; (o) the amino acid sequences of both of SEQ ID NOs: 73 and 74; (p) the amino acid sequence of SEQ ID NO: 75 (predicted sequence of α chain of 4400 TCR-A2 without N-terminal signal peptide), wherein: (i) X at position 158 of SEQ ID NO: 75 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 75 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 75 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 75 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (q) the amino acid sequence of SEQ ID NO: 76 (predicted sequence of β chain of 4400 TCR-A2 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 76 is Ser or Cys; (r) the amino acid sequences of both of SEQ ID NOs: 75 and 76; (s) the amino acid sequence of SEQ ID NO: 77 (α chain of cysteine-substituted, LVL-modified 4400 TCR-A2 with N-terminal signal peptide); (t) the amino acid sequence of SEQ ID NO: 78 (β chain of cysteine-substituted, LVL-modified 4400 TCR-A2 with N-terminal signal peptide); (u) the amino acid sequence of SEQ ID NO: 79 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-A2 without N-terminal signal peptide); (v) the amino acid sequence of SEQ ID NO: 80 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-A2 without N-terminal signal peptide); (w) the amino acid sequences of both of SEQ ID NOs: 77 and 78; (x) the amino acid sequences of both of SEQ ID NOs: 79 and 80; (y) the amino acid sequence of SEQ ID NO: 81 (α chain of 4400 TCR-E with N-terminal signal peptide), wherein: (i) X at position 177 of SEQ ID NO: 81 is Thr or Cys; (ii) X at position 241 of SEQ ID NO: 81 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 243 of SEQ ID NO: 81 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 244 of SEQ ID NO: 81 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (z) the amino acid sequence of SEQ ID NO: 82 (β chain of 4400 TCR-E with N-terminal signal peptide), wherein X at position 189 of SEQ ID NO: 82 is Ser or Cys; (aa) the amino acid sequences of both of SEQ ID NOs: 81 and 82; (bb) the amino acid sequence of SEQ ID NO: 83 (predicted sequence of α chain of 4400 TCR-E without N-terminal signal peptide), wherein: (i) X at position 160 of SEQ ID NO: 83 is Thr or Cys; (ii) X at position 224 of SEQ ID NO: 83 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 226 of SEQ ID NO: 83 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 227 of SEQ ID NO: 83 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (cc) the amino acid sequence of SEQ ID NO: 84 (predicted sequence of β chain of 4400 TCR-E without N-terminal signal peptide), wherein X at position 170 of SEQ ID NO: 84 is Ser or Cys; (dd) the amino acid sequences of both of SEQ ID NOs: 83 and 84; (ee) the amino acid sequence of SEQ ID NO: 85 (α chain of cysteine-substituted, LVL-modified 4400 TCR-E with N-terminal signal peptide); (ff) the amino acid sequence of SEQ ID NO: 86 (β chain of cysteine-substituted, LVL-modified 4400 TCR-E with N-terminal signal peptide); (gg) the amino acid sequence of SEQ ID NO: 87 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-E without N-terminal signal peptide); (hh) the amino acid sequence of SEQ ID NO: 88 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-E without N-terminal signal peptide); (ii) the amino acid sequences of both of SEQ ID NOs: 85 and 86; (jj) the amino acid sequences of both of SEQ ID NOs: 87 and 88; (kk) the amino acid sequence of SEQ ID NO: 89 (α chain of 4400 TCR-J with N-terminal signal peptide), wherein: (i) X at position 183 of SEQ ID NO: 89 is Thr or Cys; (ii) X at position 247 of SEQ ID NO: 89 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 249 of SEQ ID NO: 89 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 250 of SEQ ID NO: 89 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ll) the amino acid sequence of SEQ ID NO: 90 (β chain of 4400 TCR-J with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 90 is Ser or Cys; (mm) the amino acid sequences of both of SEQ ID NOs: 89 and 90; (nn) the amino acid sequence of SEQ ID NO: 91 (predicted sequence of α chain of 4400 TCR-J without N-terminal signal peptide), wherein: (i) X at position 161 of SEQ ID NO: 91 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 91 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 91 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 91 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (oo) the amino acid sequence of SEQ ID NO: 92 (predicted sequence of β chain of 4400 TCR-J without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 92 is Ser or Cys; (pp) the amino acid sequences of both of SEQ ID NOs: 91 and 92; (qq) the amino acid sequence of SEQ ID NO: 93 (α chain of cysteine-substituted, LVL-modified 4400 TCR-J with N-terminal signal peptide); (rr) the amino acid sequence of SEQ ID NO: 94 (β chain of cysteine-substituted, LVL-modified 4400 TCR-J with N-terminal signal peptide); (ss) the amino acid sequence of SEQ ID NO: 95 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-J without N-terminal signal peptide); (tt) the amino acid sequence of SEQ ID NO: 96 (predicted

sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-J without N-terminal signal peptide); (uu) the amino acid sequences of both of SEQ ID NOs: 93 and 94; (vv) the amino acid sequences of both of SEQ ID NOs: 95 and 96; (ww) the amino acid sequence of SEQ ID NO: 97 (α chain of 4400 TCR-N with N-terminal signal peptide), wherein: (i) X at position 178 of SEQ ID NO: 97 is Thr or Cys; (ii) X at position 242 of SEQ ID NO: 97 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 244 of SEQ ID NO: 97 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 245 of SEQ ID NO: 97 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (xx) the amino acid sequence of SEQ ID NO: 98 (β chain of 4400 TCR-N with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 98 is Ser or Cys; (yy) the amino acid sequences of both of SEQ ID NOs: 97 and 98; (zz) the amino acid sequence of SEQ ID NO: 99 (predicted sequence of α chain of 4400 TCR-N without N-terminal signal peptide), wherein: (i) X at position 157 of SEQ ID NO: 99 is Thr or Cys; (ii) X at position 221 of SEQ ID NO: 99 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 223 of SEQ ID NO: 99 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 224 of SEQ ID NO: 99 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (aaa) the amino acid sequence of SEQ ID NO: 100 (predicted sequence of β chain of 4400 TCR-N without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 100 is Ser or Cys; (bbb) the amino acid sequences of both of SEQ ID NOs: 99 and 100; (ccc) the amino acid sequence of SEQ ID NO: 101 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N with N-terminal signal peptide); (ddd) the amino acid sequence of SEQ ID NO: 102 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N with N-terminal signal peptide); (eee) the amino acid sequence of SEQ ID NO: 103 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N without N-terminal signal peptide); (fff) the amino acid sequence of SEQ ID NO: 104 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N without N-terminal signal peptide); (ggg) the amino acid sequences of both of SEQ ID NOs: 101 and 102; (hhh) the amino acid sequences of both of SEQ ID NOs: 103 and 104; (iii) the amino acid sequence of SEQ ID NO: 189 (α chain of 4400 TCR-A3 with N-terminal signal peptide), wherein: (i) X at position 176 of SEQ ID NO: 189 is Thr or Cys; (ii) X at position 240 of SEQ ID NO: 189 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 242 of SEQ ID NO: 189 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 243 of SEQ ID NO: 189 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (jjj) the amino acid sequence of SEQ ID NO: 190 (β chain of 4400 TCR-A3 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 190 is

Ser or Cys; (kkk) the amino acid sequences of both of SEQ ID NOs: 189 and 190; (lll) the amino acid sequence of SEQ ID NO: 191 (predicted sequence of α chain of 4400 TCR-A3 without N-terminal signal peptide), wherein: (i) X at position 157 of SEQ ID NO: 191 is Thr or Cys; (ii) X at position 221 of SEQ ID NO: 191 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 223 of SEQ ID NO: 191 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 224 of SEQ ID NO: 191 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (mmm) the amino acid sequence of SEQ ID NO: 192 (predicted sequence of β chain of 4400 TCR-A3 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 192 is Ser or Cys; (nnn) the amino acid sequences of both of SEQ ID NOs: 191 and 192; (ooo) the amino acid sequence of SEQ ID NO: 193 (α chain of cysteine-substituted, LVL-modified 4400 TCR-A3 with N-terminal signal peptide); (ppp) the amino acid sequence of SEQ ID NO: 194 (β chain of cysteine-substituted, LVL-modified 4400 TCR-A3 with N-terminal signal peptide); (qqq) the amino acid sequence of SEQ ID NO: 195 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-A3 without N-terminal signal peptide); (rrr) the amino acid sequence of SEQ ID NO: 196 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-A3 without N-terminal signal peptide); (sss) the amino acid sequences of both of SEQ ID NOs: 193 and 194; (ttt) the amino acid sequences of both of SEQ ID NOs: 195 and 196; (uuu) the amino acid sequence of SEQ ID NO: 197 (α chain of 4400 TCR-J2 with N-terminal signal peptide), wherein: (i) X at position 181 of SEQ ID NO: 197 is Thr or Cys; (ii) X at position 245 of SEQ ID NO: 197 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 247 of SEQ ID NO: 197 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 248 of SEQ ID NO: 197 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (vvv) the amino acid sequence of SEQ ID NO: 198 (β chain of 4400 TCR-J2 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 198 is Ser or Cys; (www) the amino acid sequences of both of SEQ ID NOs: 197 and 198; (xxx) the amino acid sequence of SEQ ID NO: 199 (predicted sequence of α chain of 4400 TCR-J2 without N-terminal signal peptide), wherein: (i) X at position 161 of SEQ ID NO: 199 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 199 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 199 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 199 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (yyy) the amino acid sequence of SEQ ID NO: 200 (predicted sequence of β chain of 4400 TCR-J2 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 200 is Ser or Cys; (zzz) the amino acid sequences of both of

SEQ ID NOs: 199 and 200; (aaaa) the amino acid sequence of SEQ ID NO: 201 (α chain of cysteine-substituted, LVL-modified 4400 TCR-J2 with N-terminal signal peptide); (bbbb) the amino acid sequence of SEQ ID NO: 202 (β chain of cysteine-substituted, LVL-modified 4400 TCR-J2 with N-terminal signal peptide); (cccc) the amino acid sequence of SEQ ID NO: 203 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-J2 without N-terminal signal peptide); (dddd) the amino acid sequence of SEQ ID NO: 204 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-J2 without N-terminal signal peptide); (eeee) the amino acid sequences of both of SEQ ID NOs: 201 and 202; (ffff) the amino acid sequences of both of SEQ ID NOs: 203 and 204; (gggg) the amino acid sequence of SEQ ID NO: 205 (α chain of 4400 TCR-N4 with N-terminal signal peptide), wherein: (i) X at position 184 of SEQ ID NO: 205 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 205 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 205 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 205 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (hhhh) the amino acid sequence of SEQ ID NO: 206 (β chain of 4400 TCR-N4 with N-terminal signal peptide), wherein X at position 190 of SEQ ID NO: 206 is Ser or Cys; (iiii) the amino acid sequences of both of SEQ ID NOs: 205 and 206; (jjjj) the amino acid sequence of SEQ ID NO: 207 (predicted sequence of α chain of 4400 TCR-N4 without N-terminal signal peptide), wherein: (i) X at position 163 of SEQ ID NO: 207 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 207 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 207 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 207 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (kkkk) the amino acid sequence of SEQ ID NO: 208 (predicted sequence of β chain of 4400 TCR-N4 without N-terminal signal peptide), wherein X at position 164 of SEQ ID NO: 208 is Ser or Cys; (llll) the amino acid sequences of both of SEQ ID NOs: 207 and 208; (mmmm) the amino acid sequence of SEQ ID NO: 209 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N4 with N-terminal signal peptide); (nnnn) the amino acid sequence of SEQ ID NO: 210 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N4 with N-terminal signal peptide); (oooo) the amino acid sequence of SEQ ID NO: 211 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N4 without N-terminal signal peptide); (pppp) the amino acid sequence of SEQ ID NO: 212 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N4 without N-terminal signal peptide); (qqqq) the amino acid sequences of both of SEQ ID NOs: 209 and 210; (rrrr) the amino acid sequences of both of SEQ ID

NOs: 211 and 212; (ssss) the amino acid sequence of SEQ ID NO: 213 (α chain of 4400 TCR-N12 with N-terminal signal peptide), wherein: (i) X at position 183 of SEQ ID NO: 213 is Thr or Cys; (ii) X at position 247 of SEQ ID NO: 213 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 249 of SEQ ID NO: 213 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 250 of SEQ ID NO: 213 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (tttt) the amino acid sequence of SEQ ID NO: 214 (β chain of 4400 TCR-N12 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 214 is Ser or Cys; (uuuu) the amino acid sequences of both of SEQ ID NOs: 213 and 214; (vvvv) the amino acid sequence of SEQ ID NO: 215 (predicted sequence of α chain of 4400 TCR-N12 without N-terminal signal peptide), wherein: (i) X at position 161 of SEQ ID NO: 215 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 215 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 215 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 215 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (www) the amino acid sequence of SEQ ID NO: 216 (predicted sequence of β chain of 4400 TCR-N12 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 216 is Ser or Cys; (xxxx) the amino acid sequences of both of SEQ ID NOs: 215 and 216; (yyyy) the amino acid sequence of SEQ ID NO: 217 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N12 with N-terminal signal peptide); (zzzz) the amino acid sequence of SEQ ID NO: 218 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N12 with N-terminal signal peptide); (aaaa) the amino acid sequence of SEQ ID NO: 219 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N12 without N-terminal signal peptide); (bbbb) the amino acid sequence of SEQ ID NO: 220 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N12 without N-terminal signal peptide); (cccc) the amino acid sequences of both of SEQ ID NOs: 217 and 218; (ddddd) the amino acid sequences of both of SEQ ID NOs: 219 and 220; (eeee) the amino acid sequence of SEQ ID NO: 221 (α chain of 4400 TCR-N13 with N-terminal signal peptide), wherein: (i) X at position 180 of SEQ ID NO: 221 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 221 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 221 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ffff) the amino acid sequence of SEQ ID NO: 222 (β chain of 4400 TCR-N13 with N-terminal signal peptide), wherein X at position 188 of SEQ ID NO: 222 is Ser or Cys; (ggggg) the amino acid sequences of both of SEQ ID NOs: 221 and 222; (hhhhh) the amino acid sequence of

SEQ ID NO: 223 (predicted sequence of α chain of 4400 TCR-N13 without N-terminal signal peptide), wherein: (i) X at position 158 of SEQ ID NO: 223 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 223 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 223 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iiii) the amino acid sequence of SEQ ID NO: 224 (predicted sequence of β chain of 4400 TCR-N13 without N-terminal signal peptide), wherein X at position 169 of SEQ ID NO: 224 is Ser or Cys; (jjjjj) the amino acid sequences of both of SEQ ID NOs: 223 and 224; (kkkkk) the amino acid sequence of SEQ ID NO: 225 (α chain of cysteine-substituted, LVL-modified 4400 TCR-N13 with N-terminal signal peptide); (lllll) the amino acid sequence of SEQ ID NO: 226 (β chain of cysteine-substituted, LVL-modified 4400 TCR-N13 with N-terminal signal peptide); (mmmmm) the amino acid sequence of SEQ ID NO: 227 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-N13 without N-terminal signal peptide); (nnnnn) the amino acid sequence of SEQ ID NO: 228 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-N13 without N-terminal signal peptide); (ooooo) the amino acid sequences of both of SEQ ID NOs: 225 and 226; (ppppp) the amino acid sequences of both of SEQ ID NOs: 227 and 228; (qqqqq) the amino acid sequence of SEQ ID NO: 229 (α chain of 4400 TCR-C with N-terminal signal peptide), wherein: (i) X at position 184 of SEQ ID NO: 229 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 229 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (rrrrr) the amino acid sequence of SEQ ID NO: 230 (β chain of 4400 TCR-C with N-terminal signal peptide), wherein X at position 189 of SEQ ID NO: 230 is Ser or Cys; (sssss) the amino acid sequences of both of SEQ ID NOs: 229 and 230; (ttttt) the amino acid sequence of SEQ ID NO: 231 (predicted sequence of α chain of 4400 TCR-C without N-terminal signal peptide), wherein: (i) X at position 163 of SEQ ID NO: 231 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 231 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 231 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (uuuuu) the amino acid sequence of SEQ ID NO: 232 (predicted sequence of β chain of 4400 TCR-C without N-terminal signal peptide), wherein X at position 170 of SEQ ID NO: 232 is Ser or Cys; (vvvvv) the amino acid sequences of both of SEQ ID NOs: 231 and 232; (wwwww) the amino acid sequence of SEQ ID NO: 233 (α

chain of cysteine-substituted, LVL-modified 4400 TCR-C with N-terminal signal peptide); (xxxxxx) the amino acid sequence of SEQ ID NO: 234 (β chain of cysteine-substituted, LVL-modified 4400 TCR-C with N-terminal signal peptide); (yyyyyy) the amino acid sequence of SEQ ID NO: 235 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-C without N-terminal signal peptide); (zzzzzz) the amino acid sequence of SEQ ID NO: 236 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-C without N-terminal signal peptide); (aaaaaa) the amino acid sequences of both of SEQ ID NOs: 233 and 234; (bbbbbb) the amino acid sequences of both of SEQ ID NOs: 235 and 236; (cccccc) the amino acid sequence of SEQ ID NO: 237 (α chain of 4400 TCR-20 with N-terminal signal peptide), wherein: (i) X at position 184 of SEQ ID NO: 237 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 237 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 237 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 237 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (dddddd) the amino acid sequence of SEQ ID NO: 238 (β chain of 4400 TCR-20 with N-terminal signal peptide), wherein X at position 189 of SEQ ID NO: 238 is Ser or Cys; (eeeeee) the amino acid sequences of both of SEQ ID NOs: 237 and 238; (ffffff) the amino acid sequence of SEQ ID NO: 239 (predicted sequence of α chain of 4400 TCR-20 without N-terminal signal peptide), wherein: (i) X at position 163 of SEQ ID NO: 239 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 239 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 239 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (gggggg) the amino acid sequence of SEQ ID NO: 240 (predicted sequence of β chain of 4400 TCR-20 without N-terminal signal peptide), wherein X at position 170 of SEQ ID NO: 240 is Ser or Cys; (hhhhhh) the amino acid sequences of both of SEQ ID NOs: 239 and 240; (iiiiii) the amino acid sequence of SEQ ID NO: 241 (α chain of cysteine-substituted, LVL-modified 4400 TCR-20 with N-terminal signal peptide); (jjjjjj) the amino acid sequence of SEQ ID NO: 242 (β chain of cysteine-substituted, LVL-modified 4400 TCR-20 with N-terminal signal peptide); (kkkkkk) the amino acid sequence of SEQ ID NO: 243 (predicted sequence of α chain of cysteine-substituted, LVL-modified 4400 TCR-20 without N-terminal signal peptide); (llllll) the amino acid sequence of SEQ ID NO: 244 (predicted sequence of β chain of cysteine-substituted, LVL-modified 4400 TCR-20 without N-terminal signal peptide); (mmmmmm) the amino acid sequences of both of SEQ ID NOs: 241 and 242; or (nnnnnn) the amino acid sequences of both of SEQ ID NOs: 243 and 244. In an embodiment of the

invention, one or more of SEQ ID NOs: 65-68, 73-76, 81-84, 89-92, 97-100, 189-192, 197-200, 205-208, 213-216, 221-224, 229-232, and 237-240 of the polypeptide are as defined in any one of Tables 2-4.

[0089] An embodiment of the invention provides a protein comprising at least one of the polypeptides described herein. By "protein" is meant a molecule comprising one or more polypeptide chains.

[0090] In an embodiment of the invention, the protein of the invention can comprise (a) 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; (b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 11-13 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 14-16; (c) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 21-23 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 24-26; (d) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 31-33 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 34-36; (e) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 41-43 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 44-46; (f) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 119-121 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 122-124; (g) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 129-131 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 132-134; (h) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 139-141 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 142-144; (i) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 149-151 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 152-154; (j) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 159-161 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 162-164; (k) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 169-171 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 172-174; or (l) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 179-181 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 182-184.

[0091] In another embodiment of the invention, (i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 7 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 8; (ii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10; (iii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18; (iv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 19 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 20; (v) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 27 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 28; (vi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 29 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 30; (vii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 37 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 38; (viii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 39 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 40; (ix) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 47 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 48; (x) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 49 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 50; (xi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 125 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 126; (xii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 127 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 128; (xiii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 135 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 136; (xiv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 137 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 138; (xv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 145 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 146; (xvi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 147 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 148; (xvii) the first polypeptide chain comprises the amino acid

sequence of SEQ ID NO: 155 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 156; (xviii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 157 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 158; (xix) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 165 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 166; (xx) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 167 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 168; (xxi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 175 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 176; (xxii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 177 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 178; (xxiii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 185 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 186; or (xxiv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 187 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 188.

[0092] 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: 59 and the second polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 60; (ii) the first polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 61 and the second polypeptide chain may further comprise the amino acid sequence of SEQ ID NO: 62; or (iii) the first polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 63 and the second polypeptide chain may comprise the amino acid sequence of SEQ ID NO: 64. In an embodiment of the invention, one or both of SEQ ID NOs: 59 and 60 of the protein are as defined in any one of Tables 2-4.

[0093] The inventive protein may comprise a full length α or β chain, as described herein with respect to other aspects of the invention. In this regard, in an embodiment of the invention, (a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 65, wherein: (i) X at position 180 of SEQ ID NO: 65 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 65 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 65 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 65 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: 66, wherein X at position 188 of SEQ ID NO: 66 is Ser or Cys; (c) both (a) and (b); (d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 67, wherein: (i) X at position 158 of SEQ ID NO: 67 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 67 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 67 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 67 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (e) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68, wherein X at position 169 of SEQ ID NO: 68 is Ser or Cys; (f) both (d) and (e); (g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69; (h) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 70; (i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 71; (j) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 72; (k) both (g) and (h); (l) both (i) and (j); (m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73, wherein: (i) X at position 180 of SEQ ID NO: 73 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 73 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 73 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 73 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (n) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74, wherein X at position 188 of SEQ ID NO: 74 is Ser or Cys; (o) both (m) and (n); (p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 75, wherein: (i) X at position 158 of SEQ ID NO: 75 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 75 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 75 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 75 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (q) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 76, wherein X at position 169 of SEQ ID NO: 76 is Ser or Cys; (r) both (p) and (q); (s) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 77; (t) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 78; (u) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 79; (v) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 80; (w) both (s) and (t); (x) both (u) and (v); (y) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 81, wherein: (i) X at position 177 of SEQ ID NO: 81 is Thr or Cys; (ii) X at position 241 of SEQ ID NO: 81 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 243 of SEQ ID NO: 81 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at

position 244 of SEQ ID NO: 81 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (z) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 82, wherein X at position 189 of SEQ ID NO: 82 is Ser or Cys; (aa) both (y) and (z); (bb) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 83, wherein: (i) X at position 160 of SEQ ID NO: 83 is Thr or Cys; (ii) X at position 224 of SEQ ID NO: 83 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 226 of SEQ ID NO: 83 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 227 of SEQ ID NO: 83 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (cc) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 84, wherein X at position 170 of SEQ ID NO: 84 is Ser or Cys; (dd) both (bb) and (cc); (ee) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85; (ff) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86; (gg) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87; (hh) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88; (ii) both (ee) and (ff); (jj) both (gg) and (hh); (kk) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 89, wherein: (i) X at position 183 of SEQ ID NO: 89 is Thr or Cys; (ii) X at position 247 of SEQ ID NO: 89 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 249 of SEQ ID NO: 89 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 250 of SEQ ID NO: 89 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (ll) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 90, wherein X at position 188 of SEQ ID NO: 90 is Ser or Cys; (mm) both (kk) and (ll); (nn) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 91, wherein: (i) X at position 161 of SEQ ID NO: 91 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 91 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 91 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 91 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (oo) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 92, wherein X at position 169 of SEQ ID NO: 92 is Ser or Cys; (pp) both (nn) and (oo); (qq) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 93; (rr) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 94; (ss) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 95; (tt) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 96; (uu) both (qq) and (rr); (vv) both (ss) and (tt); (ww) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 97, wherein: (i) X at position 178 of SEQ ID NO: 97 is Thr or Cys;

(ii) X at position 242 of SEQ ID NO: 97 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 244 of SEQ ID NO: 97 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 245 of SEQ ID NO: 97 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (xx) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 98, wherein X at position 188 of SEQ ID NO: 98 is Ser or Cys; (yy) both (ww) and (xx); (zz) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 99, wherein: (i) X at position 157 of SEQ ID NO: 99 is Thr or Cys; (ii) X at position 221 of SEQ ID NO: 99 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 223 of SEQ ID NO: 99 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 224 of SEQ ID NO: 99 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (aaa) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 100, wherein X at position 169 of SEQ ID NO: 100 is Ser or Cys; (bbb) both (zz) and (aaa); (ccc) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 101; (ddd) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 102; (eee) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 103; (fff) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 104; (ggg) both (ccc) and (ddd); (hhh) both (eee) and (fff); (iii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 189, wherein: (i) X at position 176 of SEQ ID NO: 189 is Thr or Cys; (ii) X at position 240 of SEQ ID NO: 189 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 242 of SEQ ID NO: 189 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 243 of SEQ ID NO: 189 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (jjj) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 190, wherein X at position 188 of SEQ ID NO: 190 is Ser or Cys; (kkk) both (iii) and (jjj); (lll) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 191, wherein: (i) X at position 157 of SEQ ID NO: 191 is Thr or Cys; (ii) X at position 221 of SEQ ID NO: 191 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 223 of SEQ ID NO: 191 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 224 of SEQ ID NO: 191 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (mmm) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 192, wherein X at position 169 of SEQ ID NO: 192 is Ser or Cys; (nnn) both (lll) and (mmm); (ooo) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 193; (ppp) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 194; (qqq) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 195; (rrr) the second polypeptide chain comprises the amino acid sequence of SEQ ID

NO: 196; (sss) both (ooo) and (ppp); (ttt) both (qqq) and (rrr); (uuu) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 197, wherein: (i) X at position 181 of SEQ ID NO: 197 is Thr or Cys; (ii) X at position 245 of SEQ ID NO: 197 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 247 of SEQ ID NO: 197 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 248 of SEQ ID NO: 197 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (vvv) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 198, wherein X at position 188 of SEQ ID NO: 198 is Ser or Cys; (www) both (uuu) and (vvv); (xxx) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 199, wherein: (i) X at position 161 of SEQ ID NO: 199 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 199 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 199 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 199 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (yyy) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 200, wherein X at position 169 of SEQ ID NO: 200 is Ser or Cys; (zzz) both (xxx) and (yyy); (aaaa) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 201; (bbbb) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 202; (cccc) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 203; (dddd) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 204; (eeee) both (aaaa) and (bbbb); (ffff) both (cccc) and (dddd); (gggg) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 205, wherein: (i) X at position 184 of SEQ ID NO: 205 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 205 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 205 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 205 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (hhhh) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 206, wherein X at position 190 of SEQ ID NO: 206 is Ser or Cys; (iiii) both (gggg) and (hhhh); (jjjj) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 207, wherein: (i) X at position 163 of SEQ ID NO: 207 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 207 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 207 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 207 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (kkkk) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 208, wherein X at position 164 of SEQ ID NO: 208 is Ser or Cys; (llll) both (jjjj) and (kkkk); (mmmm) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO:

209; (nnnn) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 210; (oooo) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 211; (pppp) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 212; (qqqq) both (mmmm) and (nnnn); (rrrr) both (oooo) and (pppp); (ssss) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 213, wherein: (i) X at position 183 of SEQ ID NO: 213 is Thr or Cys; (ii) X at position 247 of SEQ ID NO: 213 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 249 of SEQ ID NO: 213 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 250 of SEQ ID NO: 213 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (tttt) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 214, wherein X at position 188 of SEQ ID NO: 214 is Ser or Cys; (uuuu) both (ssss) and (tttt); (vvvv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 215, wherein: (i) X at position 161 of SEQ ID NO: 215 is Thr or Cys; (ii) X at position 225 of SEQ ID NO: 215 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 227 of SEQ ID NO: 215 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 228 of SEQ ID NO: 215 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (wwww) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 216, wherein X at position 169 of SEQ ID NO: 216 is Ser or Cys; (xxxx) both (vvvv) and (wwww); (yyyy) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 217; (zzzz) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 218; (aaaaa) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 219; (bbbbb) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 220; (ccccc) both (yyyy) and (zzzz); (ddddd) both (aaaaa) and (bbbbb); (eeee) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 221, wherein: (i) X at position 180 of SEQ ID NO: 221 is Thr or Cys; (ii) X at position 244 of SEQ ID NO: 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 246 of SEQ ID NO: 221 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 247 of SEQ ID NO: 221 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (fffff) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 222, wherein X at position 188 of SEQ ID NO: 222 is Ser or Cys; (ggggg) both (eeee) and (fffff); (hhhhh) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 223, wherein: (i) X at position 158 of SEQ ID NO: 223 is Thr or Cys; (ii) X at position 222 of SEQ ID NO: 223 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 224 of SEQ ID NO: 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 225 of SEQ ID NO: 223 is Gly, Ala, Val,

Leu, Ile, Pro, Phe, Met, or Trp; (iiii) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 224, wherein X at position 169 of SEQ ID NO: 224 is Ser or Cys; (jjjj) both (hhhh) and (iiii); (kkkk) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 225; (llll) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 226; (mmmm) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 227; (nnnn) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 228; (oooo) both (kkkk) and (llll); (pppp) both (mmmm) and (nnnn); (qqqq) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 229, wherein: (i) X at position 184 of SEQ ID NO: 229 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 229 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (rrrr) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 230, wherein X at position 189 of SEQ ID NO: 230 is Ser or Cys; (ssss) both (qqqq) and (rrrr); (tttt) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 231, wherein: (i) X at position 163 of SEQ ID NO: 231 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 231 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 231 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (uuuu) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 232, wherein X at position 170 of SEQ ID NO: 232 is Ser or Cys; (vvvv) both (tttt) and (uuuu); (wwww) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 233; (xxxx) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 234; (yyyy) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 235; (zzzz) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 236; (aaaa) both (wwww) and (xxxx); (bbbb) both (yyyy) and (zzzz); (cccc) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 237, wherein: (i) X at position 184 of SEQ ID NO: 237 is Thr or Cys; (ii) X at position 248 of SEQ ID NO: 237 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 250 of SEQ ID NO: 237 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 251 of SEQ ID NO: 237 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (dddd) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 238, wherein X at position 189 of SEQ ID NO: 238 is Ser or Cys; (eeee) both (cccc) and (dddd); (ffff) the first polypeptide

chain comprises the amino acid sequence of SEQ ID NO: 239, wherein: (i) X at position 163 of SEQ ID NO: 239 is Thr or Cys; (ii) X at position 227 of SEQ ID NO: 239 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (iii) X at position 229 of SEQ ID NO: 239 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and (iv) X at position 230 of SEQ ID NO: 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp; (gggggg) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 240, wherein X at position 170 of SEQ ID NO: 240 is Ser or Cys; (hhhhhh) both (ffffff) and (gggggg); (iiiiii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 241; (jjjjjj) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 242; (kkkkkk) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 243; (llllll) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 244; (mmmmmm) both (iiiiii) and (jjjjjj); or (nnnnnn) both (kkkkkk) and (llllll).. In an embodiment of the invention, one or more of SEQ ID NOs: 65-68, 73-76, 81-84, 89-92, 97-100, 189-192, 197-200, 205-208, 213-216, 221-224, 229-232, and 237-240 of the protein are as defined in any one of Tables 2-4.

[0094] 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 the TCR α and β chains, 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.

[0095] 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.

[0096] 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 peptide comprising the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 105). 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.

[0097] 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.

[0098] 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 G13D 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.

[0099] 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.

[0100] 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.

[0101] 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: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86,

SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 234, SEQ ID NO: 235, SEQ ID NO: 236, SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO: 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, or SEQ ID NO: 244, both of SEQ ID NOs: 65-66, both of SEQ ID NOs: 67-68, both of SEQ ID NOs: 69-70, both of SEQ ID NOs: 71-72, both of SEQ ID NOs: 73-74, both of SEQ ID NOs: 75-76, both of SEQ ID NOs: 77-78, both of SEQ ID NOs: 79-80, both of SEQ ID NOs: 81-82, both of SEQ ID NOs: 83-84, both of SEQ ID NOs: 85-86, both of SEQ ID NOs: 87-88, both of SEQ ID NOs: 89-90, both of SEQ ID NOs: 91-92, both of SEQ ID NOs: 93-94, both of SEQ ID NOs: 95-96, both of SEQ ID NOs: 97-98, both of SEQ ID NOs: 99-100, both of SEQ ID NOs: 101-102, both of SEQ ID NOs: 103-104, both of SEQ ID NOs: 189 and 190, both of SEQ ID NOs: 191 and 192, both of SEQ ID NOs: 193 and 194, both of SEQ ID NOs: 195 and 196, both of SEQ ID NOs: 197 and 198, both of SEQ ID NOs: 199 and 200, both of SEQ ID NOs: 201 and 202, both of SEQ ID NOs: 203 and 204, both of SEQ ID NOs: 205 and 206, both of SEQ ID NOs: 207 and 208, both of SEQ ID NOs: 209 and 210, both of SEQ ID NOs: 211 and 212, both of SEQ ID NOs: 213 and 214, both of SEQ ID NOs: 215 and 216, both of SEQ ID NOs: 217 and 218, both of SEQ ID NOs: 219 and 220, both of SEQ ID NOs: 221 and 222, both of SEQ ID NOs: 223 and 224, both of SEQ ID NOs: 225 and 226, both of SEQ ID NOs: 227 and 228, both of SEQ ID NOs: 229 and 230, both of SEQ ID NOs: 231 and 232, both of SEQ ID NOs: 233 and 234, both of SEQ ID NOs: 235 and 236, both of SEQ ID NOs: 237 and 238, both of SEQ ID NOs: 239 and 240, both of SEQ ID NOs: 241 and 242, or both of SEQ ID NOs: 243 and 244.

[0102] Also, for instance, the inventive TCRs, polypeptides, or proteins can consist essentially of the amino acid sequence(s) of (1) SEQ ID NO: 7, (2) SEQ ID NO: 8, (3) SEQ ID NO: 9, (4) SEQ ID NO: 10, (5) SEQ ID NO: 17, (6) SEQ ID NO: 18, (7) SEQ ID NO: 19, (8) SEQ ID NO: 20, (9) SEQ ID NO: 27, (10) SEQ ID NO: 28, (11) SEQ ID NO: 29, (12) SEQ ID NO: 30, (13) SEQ ID NO: 37, (14) SEQ ID NO: 38, (15) SEQ ID NO: 39, (16) SEQ ID NO: 40, (17) SEQ ID NO: 47, (18) SEQ ID NO: 48, (19) SEQ ID NO: 49, (20) SEQ ID NO: 50, (21) SEQ ID NO: 125, (22) SEQ ID NO: 126, (23) SEQ ID NO: 127, (24) SEQ ID NO: 128, (25) SEQ ID NO: 135, (26) SEQ ID NO: 136, (27) SEQ ID NO: 137, (28) SEQ ID NO: 138, (29) SEQ ID NO: 145, (30) SEQ ID NO: 146, (31) SEQ ID NO: 147, (32) SEQ ID NO: 148, (33) SEQ ID NO: 155, (34) SEQ ID NO: 156, (35) SEQ ID NO: 157, (36) SEQ ID NO: 158, (37) SEQ ID NO: 165, (38) SEQ ID NO: 166, (39) SEQ ID NO: 167, (40) SEQ ID NO: 168, (41) SEQ ID NO: 175, (42) SEQ ID NO: 176, (43) SEQ ID NO: 177, (44) SEQ ID NO: 178, (45) SEQ ID NO: 185, (46) SEQ ID NO: 186, (47) SEQ ID NO: 187, (48) SEQ ID NO: 188, (49) both of SEQ ID NOs: 7 and 8, (50) both of SEQ ID NOs: 9 and 10, (51) both of SEQ ID NOs: 17 and 18, (52) both of SEQ ID NOs: 19 and 20, (53) both of SEQ ID NOs: 27 and 28, (54) both of SEQ ID NOs: 29 and 30, (55) both of SEQ ID NOs: 37 and 38, (56) both of SEQ ID NOs: 39 and 40, (57) both of SEQ ID NOs: 47 and 48, (58) both of SEQ ID NOs: 49 and 50, (59) both of SEQ ID NOs: 125 and 126, (60) both of SEQ ID NOs: 127 and 128, (61) both of SEQ ID NOs: 135 and 136, (62) both of SEQ ID NOs: 137 and 138, (63) both of SEQ ID NOs: 145 and 146, (64) both of SEQ ID NOs: 147 and 148, (65) both of SEQ ID NOs: 155 and 156, (66) both of SEQ ID NOs: 157 and 158, (67) both of SEQ ID NOs: 165 and 166, (68) both of SEQ ID NOs: 167 and 168, (69) both of SEQ ID NOs: 175 and 176, (70) both of SEQ ID NOs: 177 and 178, (71) both of SEQ ID NOs: 185 and 186, or (72) both of SEQ ID NOs: 187 and 188. Furthermore, the inventive TCRs, polypeptides, or proteins can consist essentially of the amino acid sequences of (a) all of SEQ ID NOs: 1-3, (b) all of SEQ ID NOs: 4-6, (c) all of SEQ ID NOs: 1-6, (d) all of SEQ ID NOs: 11-13, (e) all of SEQ ID NOs: 14-16, (f) all of SEQ ID NOs: 11-16, (g) all of SEQ ID NOs: 21-23, (h) all of SEQ ID NOs: 24-26, (i) all of SEQ ID NOs: 21-26, (j) all of SEQ ID NOs: 31-33, (k) all of SEQ ID NOs: 34-36, (l) all of SEQ ID NOs: 31-36, (m) all of SEQ ID NOs: 41-43, (n) all of SEQ ID NOs: 44-46, (o) all of SEQ ID NOs: 41-46, (p) all of SEQ ID NOs: 119-121, (q) all of SEQ ID NOs: 122-124, (r) all of SEQ ID NOs: 119-124, (s) all of SEQ ID NOs: 129-131, (t) all of SEQ ID NOs: 132-134, (u) all of SEQ ID NOs: 129-134, (v) all of SEQ ID NOs: 139-141, (w) all of SEQ ID NOs: 142-144, (x) all of SEQ ID NOs: 139-144, (y) all of SEQ

ID NOs: 149-151, (z) all of SEQ ID NOs: 152-154, (aa) all of SEQ ID NOs: 149-154, (bb) all of SEQ ID NOs: 159-161, (cc) all of SEQ ID NOs: 162-164, (dd) all of SEQ ID NOs: 159-164, (ee) all of SEQ ID NOs: 169-171, (ff) all of SEQ ID NOs: 172-174, (gg) all of SEQ ID NOs: 169-174, (hh) all of SEQ ID NOs: 179-181, (ii) all of SEQ ID NOs: 182-184, or (jj) all of SEQ ID NOs: 179-184. 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 G13D 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.

[0103] 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-acetylaminoethyl-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.

[0104] The TCRs, polypeptides, and proteins of the invention can be 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.

[0105] 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 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 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.

[0106] 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.

[0107] 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.

[0108] 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.

[0109] In an embodiment of the invention, the nucleic acid comprises the nucleotide sequence of SEQ ID NO: 114 (4400 TCR-E), SEQ ID NO: 115 (4400 TCR-J), SEQ ID NO: 116 (4400 TCR-N), SEQ ID NO: 117 (4400 TCR-A1), or SEQ ID NO: 118 (4400 TCR-A2).

[0110] 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, N⁶-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N⁶-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, β -D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N⁶-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.

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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; 8 and 7; 9 and 10; 10 and 9; 17 and 18; 18 and 17; 19 and 20; 20 and 19; 27 and 28; 28 and 27; 29 and 30; 30 and 29; 37 and 38; 38 and 37; 39 and 40; 40 and

39; 47 and 48; 48 and 47; 49 and 50; 50 and 49; 125 and 126; 126 and 125; 127 and 128; 128 and 127; 135 and 136; 136 and 135; 137 and 138; 138 and 137; 145 and 146; 146 and 145; 147 and 148; 148 and 147; 155 and 156; 156 and 155; 157 and 158; 158 and 157; 165 and 166; 166 and 165; 167 and 168; 168 and 167; 175 and 176; 176 and 175; 177 and 178; 178 and 177; 185 and 186; 186 and 185; 187 and 188; 188 and 187; 65 and 66; 66 and 65; 67 and 68; 68 and 67; 69 and 70; 70 and 69; 71 and 72; 72 and 71; 73 and 74; 74 and 73; 75 and 76; 76 and 75; 77 and 78; 78 and 77; 79 and 80; 80 and 79; 81 and 82; 82 and 81; 83 and 84; 84 and 83; 85 and 86; 86 and 85; 87 and 88; 88 and 87; 89 and 90; 90 and 89; 91 and 92; 92 and 91; 93 and 94; 94 and 93; 95 and 96; 96 and 95; 97 and 98; 98 and 97; 99 and 100; 100 and 99; 101 and 102; 102 and 101; 103 and 104; 104 and 103; 189 and 190; 190 and 189; 191 and 192; 192 and 191; 193 and 194; 194 and 193; 195 and 196; 196 and 195; 197 and 198; 198 and 197; 199 and 200; 200 and 199; 201 and 202; 202 and 201; 203 and 204; 204 and 203; 205 and 206; 206 and 205; 207 and 208; 208 and 207; 209 and 210; 210 and 209; 211 and 212; 212 and 211; 213 and 214; 214 and 213; 215 and 216; 216 and 215; 217 and 218; 218 and 217; 219 and 220; 220 and 219; 221 and 222; 222 and 221; 223 and 224; 224 and 223; 225 and 226; 226 and 225; 227 and 228; 228 and 227; 229 and 230; 230 and 229; 231 and 232; 232 and 231; 233 and 234; 234 and 233; 235 and 236; 236 and 235; 237 and 238; 238 and 237; 239 and 240; 240 and 239; 241 and 242; 242 and 241; 243 and 244; or 244 and 243.

[0116] 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: 105).

[0117] 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.

[0118] 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.

[0119] 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 group consisting of 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 λ GT10, λ GT11, λ ZapII (Stratagene), λ EMBL4, and λ NM1149, 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.

[0120] 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 ColEI, 2 μ plasmid, λ , SV40, bovine papillomavirus, and the like.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] Another embodiment of the invention further provides a host cell comprising any of the nucleic acids or 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. 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, DH5 α *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 DH5 α 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 the group consisting of 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 MTEYKLVVVGAGDVGKSALTIQLIQ (SEQ ID NO: 252), the method comprising contacting a cell with any of the vectors described herein under conditions that allow introduction of the vector into the cell.

[0127] 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., Th₁ and Th₂ 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.

[0128] 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 cells, 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.

[0129] 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).

[0130] 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%.

[0131] 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 agents, e.g., asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, vincristine, etc.

[0132] 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.

[0133] 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.

[0134] 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 albumen.

[0135] 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., G13D 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.

[0136] 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.

[0137] 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 1×10^6 to about 1×10^{12} cells or more. In certain embodiments, fewer than 1×10^6 cells may be administered.

[0138] 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 G13D RAS or to detect, treat, or prevent cancer.

[0139] 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 G13D 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 G13D 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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*.

[0147] 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).

[0148] 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.

[0149] With respect to the inventive methods, the cancer can be any cancer, including 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 13 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 13 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.

[0150] 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, Ceboidea, or Simiiformes (monkeys) or of the order Anthropoidea (humans and apes). An especially preferred mammal is the human.

[0151] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

[0152] This example demonstrates the isolation of anti-G13D RAS TCRs from the TIL of colorectal cancer patient 4400.

[0153] TILs from tumor fragments from colorectal cancer patient 4400 were independently screened for reactivity against RAS G13D. TIL from tumor fragments (numbered F1-F8, F10-F16, and F18-F22) from patient 4400 (effector cells) were co-cultured with DC (target cells). The DC were (i) transfected with mRNA encoding full length (FL) G13D KRAS (variant B) or the corresponding FL wild-type (WT) KRAS (variant B); (ii) pulsed with G13D 25-mer peptide MTEYKLVVVGAGDVGKSALTIQLIQ (SEQ ID NO: 252) or the corresponding WT 25-mer peptide MTEYKLVVVGAGGVGKSALTIQLIQ (SEQ ID NO: 253); or (iii) cultured with G13D ME “mix” (containing a combination of three predicted minimal epitopes from the mutated peptide). Effector cells (i) co-cultured with DC treated with DMSO or (ii) cultured alone (T cell only) served as negative controls. Effector cells treated with anti-CD3/CD28 antibodies served as a positive control.

[0154] Reactivity was tested by IFN γ -secretion using ELISpot assay (Figure 1) and by measuring the expression of one or both of 4-1BB and OX40 by flow cytometry assay gated on (i) CD3⁺/CD4⁺ cells (Figure 2A) or (ii) CD3⁺/CD8⁺ cells (Figure 2B). Reactive cells were observed following co-culture of the TIL from tumor fragments F15, F16, F21, and F22 with DCs which had been pulsed with the G13D 25-mer peptide or transduced with the full length G13D KRAS protein.

[0155] Enriched populations of TIL from tumor fragments F15, F16, F21, and F22 were screened for reactivity as follows. TIL from tumor fragments F15 and F16 were untreated or treated as follows: F16 TIL were stimulated *in vitro* (IVS) with DC pulsed with G13D 25-mer peptide, or F15 and F16 TIL were combined, activated (as described for Figs. 1 and 2A-2B), sorted for CD4⁺/4-1BB⁺/OX40⁺ expression and underwent a rapid expansion protocol (REP). TIL from tumor fragments F21 and F22 were combined, sorted for

CD4⁺/41BB⁺/OX40⁺ or CD8⁺/41BB⁺/OX40⁺ expression, and underwent REP. The REP was carried out as follows. After sorting, cells were seeded in T25 flasks and rapidly expanded by adding 2e7 irradiated feeder cells in 20 ml T cell medium supplemented with 3000 IU/ml IL-2 and 30 ug/ml anti-CD3 antibody (Ab) (OKT3). Cells were grown for 11–16 days. The treated TIL were co-cultured with the target cells described for the experiments of Figures 1 and 2A-2B. The controls were also as described for the experiments of Figures 1 and 2A-2B. Reactivity was tested by measuring the expression of one or both of 4-1BB and OX40 by flow cytometry assay. The results are shown in Figure 3. Reactive cells were single-cell sorted by fluorescence activated cell sorting (FACS) into 96-well plates and were sequenced to provide TCR alpha and TCR beta chains for 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-B1, and 4400 TCR-B2.

[0156] The avidity of the enriched populations of the TIL identified as reactive in Fig. 3 was tested as follows. The TILs were co-cultured with DC pulsed with various concentrations of G13D 25-mer peptide or the corresponding WT 25-mer peptide. Reactivity was tested by IFN γ -secretion using ELISpot assay. The results are shown in Figures 4A-4B. Figure 4A shows the results obtained with TIL from tumor fragment F16 following G13D IVS (Fig. 4A). Figure 4B shows the results obtained with TIL from tumor fragments F15 and F16 following activation, sorting for CD4⁺/41BB⁺/OX40⁺ and REP (Fig. 4B).

[0157] Another four TCRs (4400 TCR-E, 4400 TCR-J, 4400 TCR-N, and TCR-C) were discovered by sorting and sequencing T cells directly from the tumor, without *in vitro* cell culture, briefly as follows. These TCR sequences were obtained by sorting T cells from a single-cell suspension of the fresh tumor digest and performing single-cell TCR sequencing coupled with RNA sequencing. 14 TCRs were selected because their transcriptional phenotype resembled those of neoantigen-reactive T cells observed in other patients. When those 14 TCR plasmids were introduced into healthy donor PBL and screened against the patient's potential neoantigens (tumor mutation-encoded peptides and tandem minigenes), four were reactive against mutant KRAS, namely 4400 TCR-E, 4400 TCR-J, 4400 TCR-N, and 4400 TCR-C.

[0158] Another TCR (TCR-20) was identified by phenotype sorting and sequencing T cells directly from the patient's peripheral blood (PBL).

[0159] Five TCRs (TCR-A3, TCR-J2, TCR-N4, TCR-N12, and TCR-N13) were identified by *in vitro*-stimulation (IVS) of the T cells directly obtained from the tumor (tumor-infiltrating T lymphocytes -TIL) or without *in vitro* cell culture.

[0160] The isolated TCRs are shown in Table 5.

TABLE 5

TCR Name	Beta Chain	Alpha Chain
4400 TCR-A1	TRBV28*01 + TRBJ2-2*01 + TRBD2*01	TRAV12-3*01/02 + TRAJ34*01
4400 TCR-A2	TRBV28*01 + TRBJ2-2*01 + TRBD2*01	TRAV12-3*01/02 + TRAJ34*01
4400 TCR-E	TRBV25-1*01 + TRBJ2-3*01	TRAV26-1*01
4400 TCR-J	TRBV28*01 + TRBJ2-2*01	TRAV12-3*01
4400 TCR-N	TRBV28*01 + TRBJ2-2*01	TRAV5*01
4400 TCR-A3	TRBV28*01 + TRBJ2-2*01 + TRBD2*01	TRAV26-2*01 + TRAJ40*01
4400 TCR-J2	TRBV28*01 + TRBJ2-2*01	TRAV9-2*01 + TRAJ28*01
4400 TCR-N4	TRBV28*01 + TRBJ1-2*01 + TRBD1*01	TRAV14/DV4*01 + TRAJ44*01
4400 TCR-N12	TRBV28*01 + TRBJ2-2*01	TRAV12-3*01 + TRAJ45*01
4400 TCR-N13	TRBV28*01 + TRBJ2-2*01	TRAV12-3*01/02 + TRAJ34*01
4400 TCR-C	TRBV28 + TRBJ1-6	TRAV14/DV4 + TRAJ44
4400 TCR-20	TRBV28*01 + TRBJ1-5*01	TRAV14/DV4*01 + TRAJ6*01

[0161] The amino acid sequences of the alpha and beta chain variable regions are shown in Table 6. The CDRs are underlined. The N-terminal signal peptides are in bold font.

TABLE 6

TCR Name	TCR chain	Amino acid sequence
4400 TCR-A1	Variable α (Predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRK GPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSAT YLCAMRANTDKLIFGTGTRLQVFP (SEQ ID NO: 7)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLFCVQDMDHENMFWYRQDPGL GLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQ TSMYLCASRLGNTGELFFGEGSRLTVL (SEQ ID NO: 8)
	Variable α	MMKSLRVLLVILWLQLSWVWSQQ KVEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRK GPELLMYTYSSGNKEDG

TCR Name	TCR chain	Amino acid sequence
	(With N-terminal signal peptide)	RFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFP (SEQ ID NO: 9)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASRLGNTGELFFGEGSRLTVL (SEQ ID NO: 10)
4400 TCR-A2	Variable α (Predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFP (SEQ ID NO: 17)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASRQGNTGELFFGEGSRLTVL (SEQ ID NO: 18)
	Variable α (With N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFP (SEQ ID NO: 19)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASRQGNTGELFFGEGSRLTVL (SEQ ID NO: 20)
4400 TCR-E	Variable α (Predicted sequence without N-terminal signal peptide)	DAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNNETNEMASLIITEDRKSSSTLILPHATLRDTAVYYCIVRVAKSGANNLFFGTGTRLTVIP (SEQ ID NO: 27)
	Variable β (Predicted sequence without N-terminal signal peptide)	EADIYQTPRYLVIGTGKKITLECSQTMGHDKMYWYQQDPGMEHLHLIHSYGVNSTEEKGDLSESTVSRIRTEHFPLTLESARPSHTSQYLCASSGLTYTDTQYFGPGTRLTVL (SEQ ID NO: 28)
	Variable α (With N-terminal signal peptide)	MRLVARVTVFLTFGTIIDAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNNETNEMASLIITEDRKSSSTLILPHATLRDTAVYYCIVRVAKSGANNLFFGTGTRLTVIP (SEQ ID NO: 29)
	Variable β (With N-terminal signal peptide)	MAIRLLCYMGFYFLGAGLMEADIYQTPRYLVIGTGKKITLECSQTMGHDKMYWYQQDPGMELHLIHSYGVNSTEEKGDLSESTVSRIRTEHFPLTLESARPSHTSQYLCASSGLTYTDTQYFGPGTRLTVL (SEQ ID NO: 30)
4400 TCR-J	Variable α (Predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMSYSGGGADGLTFGKGTHLIQP (SEQ ID NO: 37)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASSQGNTGELFFGEGSRLTVL (SEQ ID NO: 38)

TCR Name	TCR chain	Amino acid sequence
	N-terminal signal peptide)	
	Variable α (With N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAI VSLNCTYSNSAFOYFMWYRQYSRKGPPELLMYTYSSGNKEDG RFTAQVDKSSKYISLFIRDSQPSDSATYLCAMSYSGGGADGLT FGKGTHLIQ (SEQ ID NO: 39)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFILAVGLVDVKVTQSSRYLVKRTGEKVFLE CVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEG YSVSREKKERFSLILESASTNQTSMYLCASSQGNTGELFFGEGS RLTVL (SEQ ID NO: 40)
4400 TCR-N	Variable α (Predicted sequence without N-terminal signal peptide)	GEDVEQSLFSLVREGDSSVINCTYTDSSSTYLYWYKQEPGAGL QLLTYIFSNMDMKQDQRLTVLLNKKDKHLSLRIADTQTGDSAI YFCAPGGYNKLIFGAGTRLAVHP (SEQ ID NO: 47)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGL GLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQ TSMYLCASRIGNTGELFFGEGSRLTVL (SEQ ID NO: 48)
	Variable α (With N-terminal signal peptide)	MKTFAGSFLFLWLQLDCMSRGEDVEQSLFSLVREGDSSVI NCTYTDSSSTYLYWYKQEPGAGLQLLTYIFSNMDMKQDQRLT VLLNKKDKHLSLRIADTQTGDSAIYFCAPGGYNKLIFGAGTRL AVHP (SEQ ID NO: 49)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFILAVGLVDVKVTQSSRYLVKRTGEKVFLE CVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEG YSVSREKKERFSLILESASTNQTSMYLCASRIGNTGELFFGEGS RLTVL (SEQ ID NO: 50)
	Variable α (Predicted sequence without N-terminal signal peptide)	KTTQPNMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPE YVIHGLTSNVNRMASLAIAEDRKSSSTLILHRATLRDAAVYYC ILRAPSGTYKYIFGTGTRLK VLA (SEQ ID NO: 125)
4400 TCR-A3	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQD PGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILE SASTNQTSMYLCASRQGNTGELFFGEGSRLTVL (SEQ ID NO: 126)
	Variable α (With N-terminal signal peptide)	MKLVTSTVLLSLGIMGDAKTTQPNMESNEEEPVHLPCNHS TISGTDYIHWYRQLPSQGPEYVIHGLTSNVNRMASLAIAEDR KSSTLILHRATLRDAAVYYCILRAPSGTYKYIFGTGTRLK VLA (SEQ ID NO: 127)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFILAVGLVDVKVTQSSRYLVKRTGEKV FLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEK GDIPEGYSVSREKKERFSLILESASTNQTSMYLCASRQGNT GELFFGEGSRLTVL (SEQ ID NO: 128)
4400 TCR-J2	Variable α (Predicted sequence without	NSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGL QLLLKATKADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSA VYFCALRLSGAGSYQLTFGKGTKLSVIP (SEQ ID NO: 135)

TCR Name	TCR chain	Amino acid sequence
	N-terminal signal peptide)	
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILEASTNQTSMYL <u>CASSQGNTGELFFGEGSRLTVL</u> (SEQ ID NO: 136)
	Variable α (With N-terminal signal peptide)	MN YSPGLVSLILLLL GR TRGNSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGLQLLLKATKADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCALRLSGAGSYQLTFGKGT KLSVIP (SEQ ID NO: 137)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILEASTNQTSMYL <u>CASSQGNTGELFFGEGSRLTVL</u> (SEQ ID NO: 138)
4400 TCR-N4	Variable α (Predicted sequence without N-terminal signal peptide)	QKITQTQPGMFVQEKEAVTLDCITYDTSDPSYGLFWYKQPSSGEMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGDSAMYFCAMRERSGTASKLTFGTGTRLQVTL (SEQ ID NO: 145)
	Variable β (Predicted sequence without N-terminal signal peptide)	SRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILEASTNQTSMYL <u>CASSLGVGSNYGYTFGSGTRLTVV</u> (SEQ ID NO: 146)
	Variable α (With N-terminal signal peptide)	MSLSSLLKVVTASLWLGP GIAQKITQTQPGMFVQEKEAVTLDCITYDTSDPSYGLFWYKQPSSGEMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGDSAMYFCAMRERSGTASKLTFGTGTRLQVTL (SEQ ID NO: 147)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILEASTNQTSMYL <u>CASSLVGSNYGYTFGSGTRLTVV</u> (SEQ ID NO: 148)
4400 TCR-N12	Variable α (Predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMSYSGGGADGLTFGKGTHLIQP (SEQ ID NO: 155)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILEASTNQTSMYL <u>CASSTGNTGELFFGEGSRLTVL</u> (SEQ ID NO: 156)
	Variable α	MMKSLRVLLVILWLQLSWVWSQ KKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDG

TCR Name	TCR chain	Amino acid sequence
	(With N-terminal signal peptide)	RFTAQVDKSSKYISLFIRDSQPSDSATYLCAMSYSGGGADGLT FGKGTHLIQ (SEQ ID NO: 157)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLE CVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIP EYSVSREKKERFSLILESASTNQTSMYLCASSTGNTGELFFGEGS RLTVL (SEQ ID NO: 158)
4400 TCR-N13	Variable α (Predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYS RKGPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQ SDSATYLCAMRANTDKLIFGTGTRLQVFP (SEQ ID NO: 165)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGL GLRLIYFSYDVKMKEKGDIP EGYSVSREKKERFSLILESASTNQ TSMYLCASRVGNTGELFFGEGSRLTVL (SEQ ID NO: 166)
	Variable α (With N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQQ KKEVEQDPGPLSVPEGAI VSLNCTYSNSAFQYFMWYRQYSRKGPELLMYTYSSGNKEDG RFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTG TRLQVFP (SEQ ID NO: 167)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLE CVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIP EYSVSREKKERFSLILESASTNQTSMYLCASRVGNTGELFFGEGS RLTVL (SEQ ID NO: 168)
4400 TCR-C	Variable α (Predicted sequence without N-terminal signal peptide)	QKITQTQPGMFVQEKEAVTLDCITYDTS DPSYGLFWYKQPSSG EMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGD SAMYFCAMRERTGTASKLTFGTGTRLQVTL (SEQ ID NO: 175)
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGL GLRLIYFSYDVKMKEKGDIP EGYSVSREKKERFSLILESASTNQ TSMYLCASSPGTENSPLHFGNGTRLTVT (SEQ ID NO: 176)
	Variable α (With N-terminal signal peptide)	MSLSSLLKVVTASLWLGPGIAQKITQTQPGMFVQEKEAVTL DCTYDTS DPSYGLFWYKQPSSGEMIFLIYQGSYDQONATEGRY SLNFQKARKSANLVISASQLGDSAMYFCAMRERTGTASKLTF GTGTRLQVTL (SEQ ID NO: 177)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLE CVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIP EYSVSREKKERFSLILESASTNQTSMYLCASSPGTENSPLHFGNG TRLTVT (SEQ ID NO: 178)
4400 TCR-20	Variable α (Predicted sequence without	QKITQTQPGMFVQEKEAVTLDCITYDTS DPSYGLFWYKQPSSG EMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGD SAMYFCAMRERSGGSYIPTFGRGTSIVHP (SEQ ID NO: 185)

TCR Name	TCR chain	Amino acid sequence
	N-terminal signal peptide)	
	Variable β (Predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQ TSMYLCASSLGTFNQPHFGDGTRLSIL (SEQ ID NO: 186)
	Variable α (With N-terminal signal peptide)	MHLSSLLKVVTASLWLGPGIAQKITQTQPGMFVQEKEAVTL DCTYDTSDPSYGLFWYKQPSSGEMIFLIYQGSYDQQNATEGRY SLNFQKARKSANL VISASQLGDSAMYFCAMRERSGGSYIPTFG RGTSLIVHP (SEQ ID NO: 187)
	Variable β (With N-terminal signal peptide)	MAIRLLCRVAFCFLAVGLVDVKVTQSSRYLVKRTGEKVFLE CVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQ TSMYLCASSLGTFNQPHFGDG TRLSIL (SEQ ID NO: 188)

EXAMPLE 2

[0162] This example demonstrates the construction of retroviral vectors encoding the respective TCRs of Example 1.

[0163] Nucleotide sequences encoding the variable regions of the α and β chains of the 4400 TCR-A1 (SEQ ID NO: 117), 4400 TCR-A2 (SEQ ID NO: 118), 4400 TCR-E (SEQ ID NO: 114), 4400 TCR-J (SEQ ID NO: 115), 4400 TCR-N (SEQ ID NO: 116), 4400 TCR-A3, 4400 TCR-J2, 4400 TCR-N4, 4400 TCR-N12, 4400 TCR-N13, 4400 TCR-C, or 4400 TCR-20 of Table 6 were obtained and codon-optimized. The TCR β VDJ regions were fused to the mouse TCR β constant chain. The TCR α VJ regions were fused to the mouse TCR α constant chain. Without being bound to a particular theory or mechanism, it is believed that replacing the constant regions of the human TCR α and TCR β chains with the corresponding murine constant regions improves TCR expression and functionality (Cohen et al., *Cancer Res.*, 66(17): 8878-86 (2006)).

[0164] In addition, the murine TCR α and TCR β constant chains were cysteine-modified. Transmembrane hydrophobic mutations were introduced into the murine TCR α constant chain. Without being bound to a particular theory or mechanism, it is believed that these modifications result in preferential pairing of the introduced TCR chains and enhanced TCR surface expression and functionality (Cohen et al., *Cancer Res.*, 67(8):3898-903 (2007); Haga-Friedman et al., *J. Immu.*, 188: 5538-5546 (2012)). The full length α and β chains of each of the four TCRs, including these modifications to the constant region, are shown in

Table 7. In Table 7, the CDRs are underlined, and the modified amino acid residues of the constant region are underlined and in bold.

TABLE 7

SEQ ID NO:	Sequence
SEQ ID NO: 69 (Cys-substituted, LVL-modified 4400 TCR-A1 α chain with N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAIVSLNCTYSN <u>SAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFI</u> <u>RDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPR</u> <u>SQDSTLCLFTDFDSQINVPKTMESGTFITDK</u> C <u>VLDMKAMD</u> SKSNGAIAWS NQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL L VIVL RILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 70 (Cys-substituted, LVL-modified 4400 TCR-A1 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH <u>ENMFWYRQDPGLGLRLIYFSYDV</u> K <u>MKEKGD</u> IEGYSVSREKKERFSLILE SASTNQTSMYL C <u>ASRLGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPS</u> KAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGV C TDPPQAYKE SNYSYCLSSRLRVSAFVHNPRNHFRCQVQFHGLSEEDKWPEGSPKPV QNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVV MAMVKRKNS
SEQ ID NO: 71 (Cys-substituted, LVL-modified 4400 TCR-A1 α chain predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYSN S <u>AFQYFMWYRQYSRKGPPELLMY</u> <u>TYSSGNKEDGRFTAQVDKSSKYISLFI</u> <u>RDSQPSDSATYLCAMRANTDKLIF</u> <u>GTGTRLQVFPNIQNPEPAVYQLKDPR</u> <u>SQDSTLCLFTDFDSQINVPKTMES</u> <u>GTFITDK</u> C <u>VLDMKAMD</u> SKSNGAIAWSNQTSFTCQDIFKETNATYPSSDV CDATLTEKSFETDMNLFQNL L VIVL RILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 72 (Cys-substituted, LVL-modified 4400 TCR-A1 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYF <u>SYDV</u> K <u>MKEKGD</u> IEGYSVSREKKERFSLILESASTNQTSMYL C <u>ASRLGNT</u> <u>GELFFGEGSRLTVLEDLRNVTPPKVSLFEPS</u> KAEIANKQKATLVCLARGFF PDHVELSWWVNGKEVHSGV C TDPPQAYKESNYSYCLSSRLRVSAFVHN PRNHFRCQVQFHGLSEEDKWPEGSPKPVQNISAEAWGRADCGITSASY QQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 77 (Cys-substituted, LVL-modified 4400 TCR-A2 α chain with N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQQKEVEQDPGPLSVPEGAIVSLNCTYSN <u>SAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFI</u> <u>RDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPR</u> <u>SQDSTLCLFTDFDSQINVPKTMESGTFITDK</u> C <u>VLDMKAMD</u> SKSNGAIAWS NQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL L VIVL RILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 78	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH <u>ENMFWYRQDPGLGLRLIYFSYDV</u> K <u>MKEKGD</u> IEGYSVSREKKERFSLILE

SEQ ID NO:	Sequence
(Cys-substituted, LVL-modified 4400 TCR-A2 β chain with N-terminal signal peptide)	SASTNQTSMYLCASROGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPSKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 79 (Cys-substituted, LVL-modified 4400 TCR-A2 α chain predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIIVSLNCTYSNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVP CDATLTEKSFETDMNLNFNQLLVIVLRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 80 (Cys-substituted, LVL-modified 4400 TCR-A2 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASROGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPSKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 85 (Cys-substituted, LVL-modified 4400 TCR-E α chain with N-terminal signal peptide)	MRLVARVTVFLTFGTIIDAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNNETNEMASLIITEDRKSSSTLILPHATLRDTAVYYCIVRVAKSGANNLFFGTGTRLTVIPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVP CDATLTEKSFETDMNLNFNQLLVIVLRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 86 (Cys-substituted, LVL-modified 4400 TCR-E β chain with N-terminal signal peptide)	MAIRLLCYMGFYFLGAGLMEADYQTPRYLVIGTGKKITLECSQTMGHDKMYWYQQDPGMELHLIHYSYGVNSTEKGDLSSSESTVSRIRTEHFPLTLESARPSHTSQYLCASSGLTYTDTQYFGPGTRLTVLEDLRNVTPPKVSLFEPSKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 87 (Cys-substituted, LVL-modified 4400 TCR-E α chain predicted sequence without N-terminal signal peptide)	DAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNNETNEMASLIITEDRKSSSTLILPHATLRDTAVYYCIVRVAKSGANNLFFGTGTRLTVIPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVP CDATLTEKSFETDMNLNFNQLLVIVLRILLKLVAGFNLLMTLRLWSS

SEQ ID NO:	Sequence
SEQ ID NO: 88 (Cys-substituted, LVL-modified 4400 TCR-E β chain predicted sequence without N-terminal signal peptide)	EADYQTPRYLVIGTGKKITLECSQTMGHDKMYWYQQDPGMELHLIHY <u>S</u> <u>YGVNSTEK</u> GDLSSSESTVSRIRTEHFPLTLESARPSHTSQYLCASSGLTYTD TQYFGPGTRLTVLEDLRNVTPPKVSLFEPСКАEIANKQKATLVCLARGFF PDHVELSWWVNGKEVHSGV <u>C</u> TDPQAYKESNYSYCLSSRLRVSATFWHN PRNHFRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASY QQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 93 (Cys-substituted, LVL-modified 4400 TCR-J α chain with N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQKEVEQDPGPLSVPEGAIVSLNCTYSN SAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFI RDSQPSDSATYLCAMSYSGGGADGLTFGKGTHLIIQPNIQNPEPAVYQLK DPRSQDSTLCLFTDFDSQINVPKTMESGTFITDK <u>C</u> VLDMKAMD SKSNGAI AWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <u>L</u> V <u>IV</u> LRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 94 (Cys-substituted, LVL-modified 4400 TCR-J β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH ENMFYWRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILE SASTNQTSMYLCASSQNGTGELFFGEGSRLTVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGV <u>C</u> TDPQAYKE SNYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPV TONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLV VMAMVKRKNS
SEQ ID NO: 95 (Cys-substituted, LVL-modified 4400 TCR-J α chain predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYSN <u>SAFQYFMWYRQYSRKGPPELLMY</u> <u>TYSSGNKEDGRFTAQVDKSSKYISLFI</u> RDSQPSDSATYLCAMSYSGGGAD <u>GLTFGKGTHLIIQPNIQNPEPAVYQLK</u> DPRSQDSTLCLFTDFDSQINVPK MESGTFITDK <u>C</u> VLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSS DVPCDATLTEKSFETDMNLFQNL <u>L</u> V <u>IV</u> LRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 96 (Cys-substituted, LVL-modified 4400 TCR-J β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDH <u>ENMFYWRQDPGLGLRLIYF</u> <u>SYDVKMKEKGDIPGYSVSREKKERFSLILE</u> SASTNQTSMYLCASSQNGT <u>GELFFGEGSRLTVLEDLRNVTPPKVSLFEPСКАEIANKQKATLVCLARGFF</u> PDHVELSWWVNGKEVHSGV <u>C</u> TDPQAYKESNYSYCLSSRLRVSATFWHN PRNHFRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASY QQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 101 (Cys-substituted, LVL-modified 4400 TCR-N α)	MKTFAGFSFLWLQLDCMSRGEDVEQSLFLSVREGDSSVINCTYTDSS TYLYWYKQEPGAGLQLTYIFSNMDMKQDQRLTVLLNKKDKHLSRIA DTQTGDSAIYFCAPGGYNKLIFGAGTRLAVHPNIQNPEPAVYQLKDPRS QDSTLCLFTDFDSQINVPKTMESGTFITDK <u>C</u> VLDMKAMD SKSNGAI AWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <u>L</u> V <u>IV</u> LR ILLKLVAGFNLLMTLRLWSS

SEQ ID NO:	Sequence
chain with N-terminal signal peptide)	
SEQ ID NO: 102 (Cys-substituted, LVL-modified 4400 TCR-N β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH ENMFWYRQDPGLGLRLIYFSYDVKMKEKGDPIEGYSVSREKKERFSLILE SASTNQTSMYLCASRIGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAYKES NYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPVTQ NISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVM AMVKRKNS
SEQ ID NO: 103 (Cys-substituted, LVL-modified 4400 TCR-N α chain predicted sequence without N-terminal signal peptide)	GEDVEQSLFLSVREGDSSVINCTYTDSSSTLYWYKQEPGAGLQLLTYIFS NMDMKQDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAPGGYNKLIFG AGTRLAVHPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESG TFITDKCVLDMKAMDSSKNGAIAWSNQTSFTCQDIFKETNATYPSSDVPC DATLTEKSFETDMNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 104 (Cys-substituted, LVL-modified 4400 TCR-N β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYF SYDVKMKEKGDPIEGYSVSREKKERFSLILEASTNQTSMYLCASRIGNT GELFFGEGSRLTVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAYKES NYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPVTQ NISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVM AMVKRKNS
SEQ ID NO: 193 (Cys-substituted, LVL-modified 4400 TCR-A3 α chain with N-terminal signal peptide)	MKLVTSITVLLSLGIMGDAKTTQPNMESNEEEPVHLPCNHSTISGTDYIH WYRQLPSQGPEYVIHGLTSNVNRMASLAIAEDRKSSSTLILHRATLRDAA VYYCILRAPSGTYKYIFGTGTRLKVLANIQNPEPAVYQLKDPRSQDSTLC LFTDFDSQINVPKTMESGTFITDKCVLDMKAMDSSKNGAIAWSNQTSFTC QDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNLVIVLRILLKLVAG FNLLMTLRLWSS
SEQ ID NO: 194 (Cys-substituted, LVL-modified 4400 TCR-A3 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH ENMFWYRQDPGLGLRLIYFSYDVKMKEKGDPIEGYSVSREKKERFSLILE ASTNQTSMYLCASRQNGTGELFFGEGSRLTVLEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAYKES NYSYCLSSRLRVSATFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPVTQ NISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVM AMVKRKNS
SEQ ID NO: 195 (Cys-substituted, LVL-modified 4400 TCR-A3)	KTTQPNMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTS NVNRMASLAIAEDRKSSSTLILHRATLRDAAVYYCILRAPSGTYKYIFGT GTRLKVLANIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESG TFITDKCVLDMKAMDSSKNGAIAWSNQTSFTCQDIFKETNATYPSSDVPC DATLTEKSFETDMNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS

SEQ ID NO:	Sequence
α chain predicted sequence without N-terminal signal peptide)	
SEQ ID NO: 196 (Cys-substituted, LVL-modified 4400 TCR-A3 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASROGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPSCAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMA MVKRKNS
SEQ ID NO: 201 (Cys-substituted, LVL-modified 4400 TCR-J2 α chain with N-terminal signal peptide)	MNYSPLGLVSLILLLLGRTRGNSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGLQLLLKATKADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCA LR LSGAGSYQLTFGKGTKLSVIPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMDSKSNGAIAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL L VIVL RILLK VAGFNLLMTLRLWSS
SEQ ID NO: 202 (Cys-substituted, LVL-modified 4400 TCR-J2 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASSQGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPSCAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMV KRKNS
SEQ ID NO: 203 (Cys-substituted, LVL-modified 4400 TCR-J2 α chain predicted sequence without N-terminal signal peptide)	NSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYPGEGLQLLLKATKADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCA LR LSGAGSYQLTFGKGTKLSVIPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKCVLDMKAMDSKSNGAIAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL L VIVL RILLK VAGFNLLMTLRLWSS
SEQ ID NO: 204 (Cys-substituted, LVL-modified 4400 TCR-J2 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMYLCASSQGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPSCAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMA MVKRKNS
SEQ ID NO: 209	MSLSSLLKVVTASLWLGPGIAQKITQTQPGMFVQEKEAVTLDCTYDTSDP SYGLFWYKQPSSGEMIFLIYQGSYDQQNATEGRYSLNFQKARKSANLVISASQLGDSAMYFCAMRERSGTASKLTFGTGTRLQVTLNIQNPEPAVYQLK

SEQ ID NO:	Sequence
(Cys-substituted, LVL-modified 4400 TCR-N4 α chain with N-terminal signal peptide)	DPRSQDSTLCLFTDFDSQINVPKTMESGTFITDK <u>C</u> VLDMKAMDSKSNNGAI AWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL <u>L</u> V <u>I</u> VLRIILLK VAGFNLLMTLRLWSS
SEQ ID NO: 210 (Cys-substituted, LVL-modified 4400 TCR-N4 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH ENMFYWRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILE SASTNQTSMYL <u>C</u> ASSLGVGSNYGYTFGSGTRLTVVEDLRNVTPPKVSLFE PSKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGV <u>C</u> TDPQAY KESNYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKP VTQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTL VVMAMVKRKNS
SEQ ID NO: 211 (Cys-substituted, LVL-modified 4400 TCR-N4 α chain predicted sequence without N-terminal signal peptide)	QKITQTQPGMFVQEKEAVTLDCYDTS <u>D</u> PSYGLFWYKQPSSGEMIFLIYQ <u>G</u> SYDQONATEGRYSLNFQKARKSANLVISASQLGDSAMYFCAMRERSGT <u>A</u> SKLTFGTGTRLQVTLNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVP KTMESGTFITDK <u>C</u> VLDMKAMDSKSNNGAIAWSNQTSFTCQDIFKETNATY PSSDVPCDATLTEKSFETDMNLFQNL <u>L</u> V <u>I</u> VLRIILLK VAGFNLLMTLRL WSS
SEQ ID NO: 212 (Cys-substituted, LVL-modified 4400 TCR-N4 β chain predicted sequence without N-terminal signal peptide)	SRYLVKRTGEKVFLECVQDMDH <u>E</u> NMFYWRQDPGLGLRLIYFSYDVKMKEK EKGDIPGYSVSREKKERFSLILEASTNQTSMYL <u>C</u> ASSLGVGSNYGYTFG SGTRLTVVEDLRNVTPPKVSLFEPSKAEIANKQKATLVCLARGFFPDHVE LSWVNGKEVHSGV <u>C</u> TDPQAYKESNYSYCLSSRLRVSAFWHNPRNHF RCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLS ATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 217 (Cys-substituted, LVL-modified 4400 TCR-N12 α chain with N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQKQVEQDPGPLSVPEGAIVSLNCT YSNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSS KYISLFIRDSQPSDSATYL <u>C</u> AMSYSGGGADGLTFGKGTHLIIQPNIQNP EPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDK <u>C</u> VLDM KAMDSKSNNGAIAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKS FETDMNLFQNL <u>L</u> V <u>I</u> VLRIILLK VAGFNLLMTLRLWSS
SEQ ID NO: 218 (Cys-substituted, LVL-modified 4400 TCR-N12 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH <u>E</u> NMFYWRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILE SASTNQTSMYL <u>C</u> ASSTGNTGELFFEGESRLTVLEDLRNVTPPKVSLFEPSK AEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGV <u>C</u> TDPQAYKES NYSYCLSSRLRVSAFWHNPRNHFRCQVQFHGLSEEDKWPEGSPKPVTON NISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVM AMVKRKNS
SEQ ID NO: 219	QKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWYRQYSRKGPPELLMY TYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYL <u>C</u> AMSYSGGGAD <u>G</u> LTFGKGTHLIIQPNIQNPPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKT

SEQ ID NO:	Sequence
(Cys-substituted, LVL-modified 4400 TCR-N12 α chain predicted sequence without N-terminal signal peptide)	MESGTFITDK <u>C</u> VLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLNFQNL <u>LVI</u> LRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 220 (Cys-substituted, LVL-modified 4400 TCR-N12 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYF SYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASSTGNT GELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 225 (Cys-substituted, LVL-modified 4400 TCR-N13 α chain with N-terminal signal peptide)	MMKSLRVLLVILWLQLSWVWSQKEVEQDPGPLSVPEGAIVSLNCTYNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDK <u>C</u> VLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLNFQNL <u>LVI</u> LRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 226 (Cys-substituted, LVL-modified 4400 TCR-N13 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASRVGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 227 (Cys-substituted, LVL-modified 4400 TCR-N13 α chain predicted sequence without N-terminal signal peptide)	QKEVEQDPGPLSVPEGAIVSLNCTYNSAFQYFMWYRQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAMRANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDK <u>C</u> VLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLNFQNL <u>LVI</u> LRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 228 (Cys-substituted, LVL-modified 4400 TCR-N13 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFWYRQDPGLGLRLIYF SYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASRVGNT GELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS

SEQ ID NO:	Sequence
SEQ ID NO: 233 (Cys-substituted, LVL-modified 4400 TCR-C α chain with N-terminal signal peptide)	MSLSLLKVV TASLWLGP GIAQKITQTQPGMFVQEKEAVTLDCTYDTSDP SYGLFWYKQPSSGEMIFLIYQGSYDQQNATEGRYSLNFQKARKSANLVIS ASQLGDSAMYFCAMRERTGTASKLTFTGTGTRLQVTLNIQNPEPAVYQLK DPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKC VLD MKAMDSKSN GAI AWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL LV IVLRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 234 (Cys-substituted, LVL-modified 4400 TCR-C β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH ENMFYWRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILE SASTNQTSMYLCASSPGTENSPLHFGNGTRLTVTEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAYKE SNYSYCLSSRLRVSAFWHNP RNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVV MAMVKRKNS
SEQ ID NO: 235 (Cys-substituted, LVL-modified 4400 TCR-C α chain predicted sequence without N-terminal signal peptide)	QKITQTQPGMFVQEKEAVTLDCTYDTSDPSYGLFWYKQPSSGEMIFLIYQ GSYDQQNATEGRYSLNFQKARKSANLVISASQLGDSAMYFCAMRERTG TASKLTFTGTGTRLQVTLNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQIN VPKTMESGTFITDKC VLD MKAMDSKSN GAI AWSNQTSTFCQDIFKETNAT YPSSDVPCDATLTEKSFETDMNLFQNL LVIVLRILLKLVAGFNLLMTLR LWSS
SEQ ID NO: 236 (Cys-substituted, LVL-modified 4400 TCR-C β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFYWRQDPGLGLRLIYF SYDVKMKEKGDIPGYSVSREKKERFSLILEASTNQTSMYLCASSPGTE NSPLHFGNGTRLTVTEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARG FFPDHVELSWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFW HNPRNHFR CQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSA SYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS
SEQ ID NO: 241 (Cys-substituted, LVL-modified 4400 TCR-20 α chain with N-terminal signal peptide)	MHLSSLLKVV TASLWLGP GIAQKITQTQPGMFVQEKEAVTLDCTYDTSD PSYGLFWYKQPSSGEMIFLIYQGSYDQQNATEGRYSLNFQKARKSANLV SASQLGDSAMYFCAMRERSGGSYIPTFGRGTS LIVHPNIQNPEPAVYQLK DPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKC VLD MKAMDSKSN GAI AWSNQTSTFCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLFQNL LV IVLRILLKLVAGFNLLMTLRLWSS
SEQ ID NO: 242 (Cys-substituted, LVL-modified 4400 TCR-20 β chain with N-terminal signal peptide)	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDH ENMFYWRQDPGLGLRLIYFSYDVKMKEKGDIPGYSVSREKKERFSLILE SASTNQTSMYLCASSLGT FNQPHFGDGTRLSILEDLRNVTPPKVSLFEP SKAEIANKQKATLVCLARGFFPDHVELSWVNGKEVHSGVCTDPQAYKE SNYSYCLSSRLRVSAFWHNP RNHFRCQVQFHGLSEEDKWPEGSPKPV TQNISAEAWGRADCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVV MAMVKRKNS

SEQ ID NO:	Sequence
SEQ ID NO: 243 (Cys-substituted, LVL-modified 4400 TCR-20 α chain predicted sequence without N-terminal signal peptide)	QKITQTQPGMFVQEKEAVTLDCITYDTSDPSYGLFWYKQPSSGEMIFLIYQ GSYDQQNATEGRYSLNFQKARKSANLVISASQLGDSAMYFCAMRERSG GSYIPTFGRGTS LIVHPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVP KTMESGTFITDKCVLDMKAMD SKSNGAIAWSNQTSTFCQDIFKETNATY PSSDVPCDATLTEKSFETDMNLFQNL <u>LVI</u> VLRIILLK VAGFNLLMTLRL WSS
SEQ ID NO: 244 (Cys-substituted, LVL-modified 4400 TCR-20 β chain predicted sequence without N-terminal signal peptide)	DVKVTQSSRYLVKRTGEKVFLCEVQDMDHENMFWYRQDPGLGLRLIYF SYDVKMKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASSLGTF NQPOHFGDGTSLILEDLRNVTPPKVSLFEPKAEIANKQKATLVCLARG FFPDHVELSWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFW HNPRNHFRQCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSA SYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS

[0165] Nucleotide sequences encoding the variable regions of the α and β chains of the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, 4400 TCR-N, 4400 TCR-A3, 4400 TCR-J2, 4400 TCR-N4, 4400 TCR-N12, 4400 TCR-N13, 4400 TCR-C, or 4400 TCR-20 of Table 7 were independently cloned into a MSGV1-based retroviral vectors with the following expression cassette configuration: 5'NcoI-VDJ β -mC β -Furin/SerGly/P2A-VJ α -mC α -EcoRI3'. To facilitate cloning of the TCR expression cassette into the MSGV1 vector 5'NcoI site, the second amino acid in the N-terminal signal peptide of the TCRV β chain was changed to an alanine (A).

[0166] The TCR β and TCR α chains were separated by a Furin Ser/Gly P2A linker peptide (SEQ ID NO: 105). Without being bound to a particular theory or mechanism, it is believed that the linker peptide provides comparable expression efficiency of the two chains (Szymczak et al., *Nat. Biotechnol.*, 22(5):589-94 (2004)).

[0167] The TCR expression cassette of the retroviral vector encoded, from 5' to 3', the TCR β and TCR α chains separated by the linker peptide. The amino acid sequence encoded by the TCR expression cassette for each respective TCR is shown in Table 8. In Table 8, the CDRs are underlined, the constant regions are italicized, and the linker peptide is shown in bold.

TABLE 8

TCR Name	Amino acid sequence encoded by TCR Expression Cassette
4400 TCR-A1	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLFECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASRLGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLAR GFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVMMAMVKKRNSRAKRSGSGATNFSLLKQAGDVEENPGPMMKS LRVLLVILWLQLSWVWSQKKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWY RQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAM RANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPRSQDSTLCFLTFDFDSQINVPKTM ESGTFITDKCVLDMKAMDSKSNAGIAWSNQTSFTCQDIFKETNATYPSSDVPCDATLT EKSFETDMNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 108)
4400 TCR-A2	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLFECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASRQNGTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLAR GFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVMMAMVKKRNSRAKRSGSGATNFSLLKQAGDVEENPGPMMKS LRVLLVILWLQLSWVWSQKKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWY RQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAM RANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPRSQDSTLCFLTFDFDSQINVPKTM ESGTFITDKCVLDMKAMDSKSNAGIAWSNQTSFTCQDIFKETNATYPSSDVPCDATLT EKSFETDMNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 109)
4400 TCR-E	MAIRLLCYMGFYFLGAGLMEADYIQTPLYLVIGTGKKITLECSQTMGHDKMYW YQQDPGMELHLIHYSYGVNSTEKGDLSSSESTVSRIRTEHFP LTLESARPSHTSQYL CASSGLTYTDTQYFGPGTRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLAR GFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVMMAMVKKRNSRAKRSGSGATNFSLLKQAGDVEENPGPMMRLV ARVTVFLTFGTIIDAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQ GPQYIIHGLKNNETNEMASLIITEDRKSSSTLILPHATLRDTAVVYCVIRVAKSGAN NLFFGTGTRLTVIPNIQNPEPAVYQLKDPRSQDSTLCFLTFDFDSQINVPKTMESGTFIT DKCVLDMKAMDSKSNAGIAWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETD MNLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 110)
4400 TCR-J	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLFECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASSOGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLAR GFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVMMAMVKKRNSRAKRSGSGATNFSLLKQAGDVEENPGPMMKS LRVLLVILWLQLSWVWSQKKEVEQDPGPLSVPEGAIVSLNCTYSNSAFQYFMWY RQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAM SYSGGGADGLTFGKGTHLIIQPNIQNPEPAVYQLKDPRSQDSTLCFLTFDFDSQINVPK TMESGTFITDKCVLDMKAMDSKSNAGIAWSNQTSFTCQDIFKETNATYPSSDVPCDAT LTEKSFETDMNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 111)
4400 TCR-N	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLFECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASRIGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPKAEIANKQKATLVCLARG FFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNP RNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG ATLYAVLVSTLVMMAMVKKRNSRAKRSGSGATNFSLLKQAGDVEENPGPMKTF GFSFLFLWLQLDCMSRGEDVEQSLFLSVREGDSSVINCTYTDSSSTYL YWYKQEP GAGLQLLTYIFSNMDMKQDQRLTVLLNKKDKHLSLRIADTQTGDSAIYFCAPGG YNKLIFGAGTRLAVHPNIQNPEPAVYQLKDPRSQDSTLCFLTFDFDSQINVPKTMESG

TCR Name	Amino acid sequence encoded by TCR Expression Cassette
	<i>TFITDKCVLDMKAMDSKSNAGALAWSNQTSTFTCQDIFKETNATYPSSDVPCDATLTEKS FETDMNLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 112)</i>
4400 TCR-A3	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASROGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPСКАEIANKQKATLVCLAR GFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMKL TSITVLLSLGIMGDAKTTQPNMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQG PEYVIHGLTSNVNNRMASLAIAEDRKSSTLILHRATLRDAAVYYCILRAPSGTYK YIFGTGTRLKVLANIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFIT DKCVLDMKAMDSKSNAGALAWSNQTSTFTCQDIFKETNATYPSSDVPCDATLTEKSFETD MNLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 245)
4400 TCR-J2	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASSOGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPСКАEIANKQKATLVCLAR GFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMNYS PGLVSLILLLLGRTRGNSVTQMEGPVTLSEEAFLTINCTYTATGYPSLFWYVQYP GEGQLQLLKATKADDKGSNKGFEATYRKETTSFHLEKGSVQVSDSAVYFCALRL SGAGSYQLTFGKGTKLSVIPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPK MESGTFITDKCVLDMKAMDSKSNAGALAWSNQTSTFTCQDIFKETNATYPSSDVPCDATL TEKSFETDMNLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 246)
4400 TCR-N4	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASSLGVSNGYGYTFGSGTRLTVVEDLRNVTPPKVSLFEPСКАEIANKQKATLVCL ARGFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNH FRCQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEIL LGKATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMS LSSLLKVVTASLWLGPIAQKITQTQPGMFVQEKEAVTLDCTYDTSDPYGLFW YKQPSSGEMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGDSAMYF CAMRERSGTASKLTFGTGTRLQVTLNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQI NVPKTMESGTFITDKCVLDMKAMDSKSNAGALAWSNQTSTFTCQDIFKETNATYPSSDV CDATLTEKSFETDMNLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 247)
4400 TCR-N12	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASSTGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPСКАEIANKQKATLVCLARG FFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMMKSL RVLLVILWLQLSWVWSQQKEVEQDPGLSVPEGAIVSLNCTYSNSAFQYFMWY RQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAM SYSGGGADGLTFGKGTHLIIQPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPK TMESGTFITDKCVLDMKAMDSKSNAGALAWSNQTSTFTCQDIFKETNATYPSSDVPCDAT LTEKSFETDMNLNFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 248)
4400 TCR-N13	MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMDHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASRVGNTGELFFGEGSRLTVLEDLRNVTPPKVSLFEPСКАEIANKQKATLVCLAR GFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPRNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMMKS LRVLLVILWLQLSWVWSQQKEVEQDPGLSVPEGAIVSLNCTYSNSAFQYFMWY RQYSRKGPPELLMYTYSSGNKEDGRFTAQVDKSSKYISLFIRDSQPSDSATYLCAM RANTDKLIFGTGTRLQVFPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTM

TCR Name	Amino acid sequence encoded by TCR Expression Cassette
	<i>ESGTFITDKCVLDMKAMDSKSNALAWSNQTSFTCQDIFKETNATYPSSDVPCDATLT EKSFEEDMNLNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 249)</i>
4400 TCR-C	<i>MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASSPGTENSPLHFGNGTRLTVTEDLRNVTPPKVSLFEPSKAEIANKQKATLVCLAR GFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFFWHNPRNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMSLS SLLKVVTASLWLGPIAQKITQTQPGMFVQEKEAVTLDCTYDTSFPSYGLFWYK QPSSGEMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGDSAMYFCA MRERTGTASKLTFGTGTRLQVTLNIQNPEPAVYQLKDPQSQDSTLCLFTDFDSQINV PKTMESGTFITDKCVLDMKAMDSKSNALAWSNQTSFTCQDIFKETNATYPSSDVPCD ATLTEKSFETDMNLNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 250)</i>
4400 TCR-20	<i>MAIRLLCRVAFCLAVGLVDVKVTQSSRYLVKRTGEKVFLECVQDMHENMFW YRQDPGLGLRLIYFSYDVKMKEKGDIPEGYSVSREKKERFSLILESASTNQTSMY LCASSLGTENQPHFGDGTRLSEDLRNVTPPKVSLFEPSKAEIANKQKATLVCLAR GFFPDHVELSWVWNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSAFFWHNPRNHFR CQVQFHGLSEEDKWPEGSPKPVTONISAEAWGRADCGITSASYQQGVLSATILYEILLG KATLYAVLVSTLVVMAMVKKNSRAKRSGSGATNFSLLKQAGDVEENPGPMHLS SLLKVVTASLWLGPIAQKITQTQPGMFVQEKEAVTLDCTYDTSFPSYGLFWYK QPSSGEMIFLIYQGSYDQONATEGRYSLNFQKARKSANLVISASQLGDSAMYFCA MRERSGGSYIPTFGRGTSLIVHPNIQNPEPAVYQLKDPQSQDSTLCLFTDFDSQINV KTMESGTFITDKCVLDMKAMDSKSNALAWSNQTSFTCQDIFKETNATYPSSDVPCDA TLTEKSFETDMNLNLFQNLVIVLRILLKLVAGFNLLMTLRLWSS (SEQ ID NO: 251)</i>

EXAMPLE 3

[0168] This example demonstrates that Jurkat cells transfected with mRNA encoding the 4400 TCR-A1 or 4400 TCR-A2 of Example 2 specifically recognize G13D.

[0169] Effector cells were a Jurkat cell line stably expressing luciferase under the transcriptional control of an NFAT promoter and also stably expressing the CD4 co-receptor. These cells were virally transduced with mRNA encoding a TCR alpha and beta chain generated according to the sequencing described for Fig. 3 (Example 1). The TCR was the 4400 TCR-A1 or 4400 TCR-A2 of Example 2 or the 4400 TCR-B1 or 4400 TCR-B2 identified in Example 1.

[0170] Transcription under the control of an NFAT promoter is activated by TCR stimulation. TCR stimulation increases intracellular calcium concentration and activates calcium channels. It is believed that the NFAT protein is then dephosphorylated by calmodulin and translocates to the nucleus where it binds with the NFAT promoter sequence and activates downstream gene expression. By providing luciferase under the transcriptional control of an NFAT promoter, luciferase is expected to be expressed only when the TCR is stimulated by the target antigen.

[0171] Target cells were DC (i) transfected with full length G13D KRAS mRNA (G13D FL) (variant B) or the corresponding full length WT KRAS mRNA (WT FL) (variant B); (ii)

pulsed with the G13D 25-mer peptide (G13D Mut LP) or the corresponding WT 25-mer peptide (G13 WT LP) of Example 1. Transfected cells co-cultured with DC treated with DMSO and Jurkat cells without TCR transfection served as negative controls.

[0172] The effector cells were co-cultured with target cells. Luciferase expression was measured by measuring luminescence units (Fig. 5). The results show that Jurkat cells transfected with 4400 TCR-A1 or 4400 TCR-A2 specifically recognize G13D.

EXAMPLE 4

[0173] This example demonstrates that healthy donor PBL independently transduced with the retroviral vector encoding the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, or 4400 TCR-N of Example 2 specifically recognize G13D.

[0174] Effector cells were healthy donor PBL independently transduced with the retroviral vector encoding the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, or 4400 TCR-N of Example 2 or the 4400 TCR-B1 or 4400 TCR-B2.

[0175] Target cells were DC (i) transduced with full length G13D KRAS mRNA (G13D FL) (variant B) or the corresponding full length WT KRAS mRNA (WT FL) (variant B); (ii) pulsed with G13D 25-mer peptide (G13D Mut LP) or the corresponding WT 25-mer peptide (G13 WT LP) of Example 1; or (iii) pulsed with G12D 25-mer peptide (G12D Mut LP) or G12V 25-mer peptide (G12V Mut LP).

[0176] The effector cells were co-cultured with the target cells. Reactivity was tested by IFN γ -secretion using ELISpot assay (Figure 6) and by measuring the expression of one or both of 4-1BB and OX40 by flow cytometry assay gated on (i) CD3⁺/mTCR⁺/CD8⁺ cells (Figure 7A) or (ii) CD3⁺/mTCR⁺/CD4⁺ cells (Figure 7B).

EXAMPLE 5

[0177] This example demonstrates that the TCRs expressed by the retroviral vectors of Example 2 recognize G13D RAS presented by a HLA-DQ heterodimer.

[0178] The MHC Class II molecules expressed by Patient 4400 were determined using exome and mRNA sequencing. The expressed MHC Class II molecules are shown in Figure 8.

[0179] HEK cells (target cells) were untransfected (control) or independently transfected with the HLA heterodimers shown in Figure 8 (alpha and beta) and then were pulsed with the G13D 25-mer peptide of Example 1. The effector cells were healthy donor PBL

independently transduced with the retroviral vector encoding the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, or 4400 TCR-N of Example 2. Effector cells cultured in the presence of anti-CD3/anti-CD28 Dynabeads served as a positive control. Reactivity was tested by IFN γ -secretion using ELISpot assay (Figure 8) and by measuring the expression of one or both of 4-1BB and OX40 by flow cytometry assay gated on CD3⁺/mTCR⁺/CD4⁺ cells (Figure 9).

[0180] As shown in Figures 8-9, reactivity was observed upon co-culture of the effector cells with target cells transduced with the HLA-DQA1*05:01/HLA-DQB1*03:01 heterodimer.

EXAMPLE 6

[0181] This example demonstrates the avidity of the TCRs expressed by the retroviral vectors of Example 2.

[0182] Healthy donor PBL (effector cells) were independently transduced with the retroviral vector of Example 2 encoding the 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, 4400 TCR-J, or 4400 TCR-N.

[0183] Autologous DCs (target cells) were loaded with the G13D 25-mer peptide or the corresponding WT 25-mer peptide of Example 1 at one of the various concentrations shown in Figures 10A-10C, 11A-11C, 12A-12C, 13A-13C, and 14A-14C. The cells were washed twice and co-cultured overnight with transduced cells at a ratio of 6e4 DC : 5e4 T cells. Reactivity was tested by IFN γ -secretion using ELISpot assay (Figures 10A, 11A, 12A, 13A, and 14A) and by measuring the expression of one or both of 4-1BB and OX40 by flow cytometry assay gated on CD3⁺/mTCR⁺/CD4⁺ cells (Figures 10B, 11B, 12B, 13B, and 14B) or gated on CD3⁺/mTCR⁺/CD8⁺ cells (Figures 10C, 11C, 12C, 13C, and 14C).

EXAMPLE 7

[0184] This example demonstrates that Jurkat cells transfected with 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-A3, 4400 TCR-E, 4400 TCR-J2, 4400 TCR-N4, 4400 TCR-N12, or 4400 TCR-N13 of Example 2 specifically recognize G13D.

[0185] Effector cells were a Jurkat-NFAT-firefly luciferase CD4⁺/CD8⁺ cell line (described in Example 3) independently virally transduced with a retroviral vector encoding or one of the following TCRs described in Example 2: 4400 TCR-A1, 4400 TCR-A2, 4400

TCR-E, 4400 TCR-A3, 4400 TCR-J, 4400 TCR-J2, 4400 TCR-N, 4400 4400 TCR-N4, 4400 TCR-N12, or 4400 TCR-N13.

[0186] Target cells were DC autologous to Patient 4400 (i) transfected overnight with full length G13D KRAS mRNA (G13D FL) (variant B) or the corresponding full length WT KRAS mRNA (WT FL) (variant B); (ii) pulsed with the G13D 25-mer peptide (G13D Mut LP) or the corresponding WT 25-mer peptide (G13 WT LP) of Example 1. Mock transduction was used as a negative control.

[0187] Effector cells were co-cultured with target cells for 5 hours followed by lysis in the presence of luciferin reagent. Luminescence was then measured as described in Example 3. The results are shown in Figure 15. The results show that Jurkat-NFAT firefly luciferase cells transfected with 4400 TCR-A1, 4400 TCR-A2, 4400 TCR-E, TCR-J, 4400 TCR-A3, 4400 TCR-J2, 4400 TCR-N, 4400 4400 TCR-N4, 4400 TCR-N12, or 4400 TCR-N13 specifically recognize G13D.

EXAMPLE 8

[0188] This example demonstrates that the TCRs expressed by the retroviral vectors of Example 2 recognize G13D RAS presented by a HLA-DQ heterodimer.

[0189] The MHC Class II molecules expressed by Patient 4400 were determined using exome and mRNA sequencing. The expressed MHC Class II molecules are shown in Figure 16.

[0190] COS7 cells (target cells) were independently transfected with the HLA heterodimers shown in Figure 16 (alpha and beta) or with HLA DRA1 only and then were pulsed with the G13D 25-mer peptide of Example 1. The effector cells were the same as those described in Example 7. Effector cells were co-cultured with target cells for 5 hours. The cells were then tested for luciferase activity, as explained in Example 3. Untransduced Jurkat-NFAT firefly luciferase cells co-cultured with the same target cells served as a negative control. The results are shown in Figure 16. As shown in Figure 16, reactivity was observed upon co-culture of the effector cells with target cells transduced with the HLA-DQA1*05:01/HLA-DQB1*03:01 heterodimer.

EXAMPLE 9

[0191] This example demonstrates the avidity of the TCRs expressed by the retroviral vectors of Example 2.

[0192] The effector cells were the same as those described in Example 7. Target cells were DCs autologous to Patient 4400 loaded with the G13D 25-mer peptide or the corresponding WT 25-mer peptide of Example 1 at one of the various concentrations shown in Figures 17A-17K. The cells were washed twice and co-cultured for 5 hours with the effector cells at a ratio of 6e4 target cells : 1.5e5 effector cells. The cells were then tested for luciferase activity, as explained in Example 3.

[0193] The results are shown in Figures 17A-17J. Figure 17K shows the results obtained following a control experiment, namely the same experiment as that which was carried out for Figures 17A-17J, except that the Jurkat-NFAT firefly luciferase cell line was virally transduced with a control plasmid (a backbone plasmid without the gene encoding a TCR). The results showed that the cells transduced with 4400 TCR-A1 (17A), 4400 TCR-A2 (17B), 4400 TCR-A3 (17C), 4400 TCR-J (17D), 4400 TCR-J2 (17E), 4400 TCR-E (17F), 4400 TCR-N (17G), 4400 TCR-N4 (17H), 4400 TCR-N12 (17I), or 4400 TCR-N13 (17J) specifically and avidly recognize G13D.

EXAMPLE 10

[0194] This example demonstrates that the 4400 TCR-C and 4400 TCR-20 expressed by the retroviral vectors of Example 2 recognize G13D RAS presented by a HLA-DQ heterodimer.

[0195] COS7 cells (target cells) were transfected with the HLA-DQA1*05:01 and HLA-DQB1*03:01 heterodimer and then were pulsed with the G13D 25-mer peptide of Example 1. Effector cells were a Jurkat-NFAT-firefly luciferase CD4⁺/CD8⁺ cell line (described in Example 3) independently virally transduced with a retroviral vector encoding the 4400 TCR-C or 4400 TCR-20 described in Example 2. Effector cells were co-cultured with target cells for 5 hours. The cells were then tested for luciferase activity, as explained in Example 3. The effector cells were co-cultured with untransfected COS7 loaded with G13D 25-mer peptide as a negative control. The results are shown in Figure 18. As shown in Figure 18, reactivity was observed upon co-culture of the effector cells with target cells transduced with the HLA-DQA1*05:01/HLA-DQB1*03:01 heterodimer.

EXAMPLE 11

[0196] This example demonstrates that healthy donor PBL independently transduced with the retroviral vector encoding the 4400 TCR-C or 4400 TCR-20 of Example 2 specifically recognize G13D.

[0197] Effector cells were healthy donor PBL independently transduced with the retroviral vector encoding the 4400 TCR-C or 4400 TCR-20 of Example 2. Target cells were autologous DC pre-loaded with G13D 25-mer peptide (G13D) or the corresponding WT 25-mer peptide of Example 1 at one of the various concentrations shown in Figures 19A-19D. The target cells were washed twice and co-cultured overnight with the effector cells at a ratio of 6e4 target cells : 1e5 effector cells.

[0198] Reactivity was tested by measuring the expression of one or both of 4-1BB and OX40 by flow cytometry assay gated on (i) CD3+/mTCR+/CD8+ cells (Figures 19B and 19D) or (ii) CD3+/mTCR+/CD4+ cells (Figures 19A and 19C).

[0199] The results showed that PBL independently transduced with the retroviral vector encoding the 4400 TCR-C (Figures 19A-19B) or 4400 TCR-20 (Figures 19C-19D) of Example 2 specifically recognized G13D.

[0200] 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.

[0201] 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.

[0202] 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.

CLAIM(S):

1. An isolated or purified T-cell receptor (TCR) having antigenic specificity for a mutated human RAS amino acid sequence with a substitution of glycine at position 13 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 13 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 of claim 1 comprising the amino acid sequences of:

- (a) all of SEQ ID NOs: 1-3,
- (b) all of SEQ ID NOs: 4-6,
- (c) all of SEQ ID NOs: 1-6,
- (d) all of SEQ ID NOs: 11-13,
- (e) all of SEQ ID NOs: 14-16,
- (f) all of SEQ ID NOs: 11-16,
- (g) all of SEQ ID NOs: 21-23,
- (h) all of SEQ ID NOs: 24-26,
- (i) all of SEQ ID NOs: 21-26,
- (j) all of SEQ ID NOs: 31-33,
- (k) all of SEQ ID NOs: 34-36,
- (l) all of SEQ ID NOs: 31-36,
- (m) all of SEQ ID NOs: 41-43,
- (n) all of SEQ ID NOs: 44-46,
- (o) all of SEQ ID NOs: 41-46
- (p) all of SEQ ID NOs: 119-121,
- (q) all of SEQ ID NOs: 122-124,
- (r) all of SEQ ID NOs: 119-124,
- (s) all of SEQ ID NOs: 129-131,

- (t) all of SEQ ID NOs: 132-134,
- (u) all of SEQ ID NOs: 129-134,
- (v) all of SEQ ID NOs: 139-141,
- (w) all of SEQ ID NOs: 142-144,
- (x) all of SEQ ID NOs: 139-144,
- (y) all of SEQ ID NOs: 149-151,
- (z) all of SEQ ID NOs: 152-154,
- (aa) all of SEQ ID NOs: 149-154,
- (bb) all of SEQ ID NOs: 159-161,
- (cc) all of SEQ ID NOs: 162-164,
- (dd) all of SEQ ID NOs: 159-164,
- (ee) all of SEQ ID NOs: 169-171,
- (ff) all of SEQ ID NOs: 172-174,
- (gg) all of SEQ ID NOs: 169-174,
- (hh) all of SEQ ID NOs: 179-181,
- (ii) all of SEQ ID NOs: 182-184, or
- (jj) all of SEQ ID NOs: 179-184.

3. The TCR according to claim 1 or 2, wherein the mutated human RAS amino acid sequence is MTEYKLVVVGAGDVGKSALTIQLIQ (SEQ ID NO: 252).

4. The TCR according to any one of claims 1-3, wherein the TCR does not have antigenic specificity for the wild-type human RAS amino acid sequence of MTEYKLVVVGAGGVGKSALTIQLIQ (SEQ ID NO: 253).

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

6. The TCR according to claim 5, wherein the HLA Class II molecule is an HLA-DQ heterodimer.

7. The TCR according to claim 5, wherein the HLA Class II molecule is an HLA-DQA1:HLA-DQB1 heterodimer.

8. The TCR according to claim 5, wherein the HLA Class II molecule is an HLA-DQA1*05:01:HLA-DQB1*03:01 heterodimer.

9. The TCR according to any one of claims 1-8, comprising the amino acid sequence(s) of:

- (1) SEQ ID NO: 7,
- (2) SEQ ID NO: 8,
- (3) SEQ ID NO: 9,
- (4) SEQ ID NO: 10,
- (5) SEQ ID NO: 17,
- (6) SEQ ID NO: 18,
- (7) SEQ ID NO: 19,
- (8) SEQ ID NO: 20,
- (9) SEQ ID NO: 27,
- (10) SEQ ID NO: 28,
- (11) SEQ ID NO: 29,
- (12) SEQ ID NO: 30,
- (13) SEQ ID NO: 37,
- (14) SEQ ID NO: 38,
- (15) SEQ ID NO: 39,
- (16) SEQ ID NO: 40,
- (17) SEQ ID NO: 47,
- (18) SEQ ID NO: 48,
- (19) SEQ ID NO: 49,
- (20) SEQ ID NO: 50,
- (21) SEQ ID NO: 125,
- (22) SEQ ID NO: 126,
- (23) SEQ ID NO: 127,
- (24) SEQ ID NO: 128,
- (25) SEQ ID NO: 135,

- (26) SEQ ID NO: 136,
- (27) SEQ ID NO: 137,
- (28) SEQ ID NO: 138,
- (29) SEQ ID NO: 145,
- (30) SEQ ID NO: 146,
- (31) SEQ ID NO: 147,
- (32) SEQ ID NO: 148,
- (33) SEQ ID NO: 155,
- (34) SEQ ID NO: 156,
- (35) SEQ ID NO: 157,
- (36) SEQ ID NO: 158,
- (37) SEQ ID NO: 165,
- (38) SEQ ID NO: 166,
- (39) SEQ ID NO: 167,
- (40) SEQ ID NO: 168,
- (41) SEQ ID NO: 175,
- (42) SEQ ID NO: 176,
- (43) SEQ ID NO: 177,
- (44) SEQ ID NO: 178,
- (45) SEQ ID NO: 185,
- (46) SEQ ID NO: 186,
- (47) SEQ ID NO: 187,
- (48) SEQ ID NO: 188,
- (49) both of SEQ ID NOs: 7 and 8,
- (50) both of SEQ ID NOs: 9 and 10,
- (51) both of SEQ ID NOs: 17 and 18,
- (52) both of SEQ ID NOs: 19 and 20,
- (53) both of SEQ ID NOs: 27 and 28,
- (54) both of SEQ ID NOs: 29 and 30,
- (55) both of SEQ ID NOs: 37 and 38,
- (56) both of SEQ ID NOs: 39 and 40,
- (57) both of SEQ ID NOs: 47 and 48,
- (58) both of SEQ ID NOs: 49 and 50,

- (59) both of SEQ ID NOs: 125 and 126,
- (60) both of SEQ ID NOs: 127 and 128,
- (61) both of SEQ ID NOs: 135 and 136,
- (62) both of SEQ ID NOs: 137 and 138,
- (63) both of SEQ ID NOs: 145 and 146,
- (64) both of SEQ ID NOs: 147 and 148,
- (65) both of SEQ ID NOs: 155 and 156,
- (66) both of SEQ ID NOs: 157 and 158,
- (67) both of SEQ ID NOs: 165 and 166,
- (68) both of SEQ ID NOs: 167 and 168,
- (69) both of SEQ ID NOs: 175 and 176,
- (70) both of SEQ ID NOs: 177 and 178,
- (71) both of SEQ ID NOs: 185 and 186, or
- (72) both of SEQ ID NOs: 187 and 188.

10. The TCR of any one of claims 1-9, further comprising:

(a) the amino acid sequence of SEQ ID NO: 59, wherein:

(i) X at position 48 of SEQ ID NO: 59 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 59 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 59 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 59 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 60, wherein X at position 57 of SEQ ID NO: 60 is Ser or Cys; or

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

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

(a) the amino acid sequence of SEQ ID NO: 65, wherein:

(i) X at position 180 of SEQ ID NO: 65 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 65 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 65 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 65 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 66, wherein X at position 188 of SEQ ID NO: 66 is Ser or Cys;

(c) both (a) and (b);

(d) the amino acid sequence of SEQ ID NO: 67, wherein:

(i) X at position 158 of SEQ ID NO: 67 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 67 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 67 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 67 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(e) the amino acid sequence of SEQ ID NO: 68, wherein X at position 169 of SEQ ID NO: 68 is Ser or Cys;

(f) both (d) and (e);

(g) the amino acid sequence of SEQ ID NO: 69;

(h) the amino acid sequence of SEQ ID NO: 70;

(i) the amino acid sequence of SEQ ID NO: 71;

(j) the amino acid sequence of SEQ ID NO: 72;

(k) both (g) and (h);

(l) both (i) and (j);

(m) the amino acid sequence of SEQ ID NO: 73, wherein:

(i) X at position 180 of SEQ ID NO: 73 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 73 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 73 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 73 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(n) the amino acid sequence of SEQ ID NO: 74, wherein X at position 188 of SEQ ID NO: 74 is Ser or Cys;

(o) both (m) and (n);

(p) the amino acid sequence of SEQ ID NO: 75, wherein:

(i) X at position 158 of SEQ ID NO: 75 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 75 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 75 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 75 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(q) the amino acid sequence of SEQ ID NO: 76, wherein X at position 169 of SEQ ID NO: 76 is Ser or Cys;

(r) both (p) and (q);

(s) the amino acid sequence of SEQ ID NO: 77;

(t) the amino acid sequence of SEQ ID NO: 78;

(u) the amino acid sequence of SEQ ID NO: 79;

(v) the amino acid sequence of SEQ ID NO: 80;

(w) both (s) and (t);

(x) both (u) and (v);

(y) the amino acid sequence of SEQ ID NO: 81, wherein:

(i) X at position 177 of SEQ ID NO: 81 is Thr or Cys;

(ii) X at position 241 of SEQ ID NO: 81 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 243 of SEQ ID NO: 81 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 244 of SEQ ID NO: 81 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(z) the amino acid sequence of SEQ ID NO: 82, wherein X at position 189 of SEQ ID NO: 82 is Ser or Cys;

(aa) both (y) and (z);

(bb) the amino acid sequence of SEQ ID NO: 83, wherein:

(i) X at position 160 of SEQ ID NO: 83 is Thr or Cys;

(ii) X at position 224 of SEQ ID NO: 83 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 226 of SEQ ID NO: 83 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 227 of SEQ ID NO: 83 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(cc) the amino acid sequence of SEQ ID NO: 84, wherein X at position 170 of SEQ ID NO: 84 is Ser or Cys;

(dd) both (bb) and (cc);

(ee) the amino acid sequence of SEQ ID NO: 85;

(ff) the amino acid sequence of SEQ ID NO: 86;

(gg) the amino acid sequence of SEQ ID NO: 87;

(hh) the amino acid sequence of SEQ ID NO: 88;

(ii) both (ee) and (ff);

(jj) both (gg) and (hh);

(kk) the amino acid sequence of SEQ ID NO: 89, wherein:

(i) X at position 183 of SEQ ID NO: 89 is Thr or Cys;

(ii) X at position 247 of SEQ ID NO: 89 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 249 of SEQ ID NO: 89 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 250 of SEQ ID NO: 89 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ll) the amino acid sequence of SEQ ID NO: 90, wherein X at position 188 of SEQ ID NO: 90 is Ser or Cys;

(mm) both (kk) and (ll);

(nn) the amino acid sequence of SEQ ID NO: 91, wherein:

(i) X at position 161 of SEQ ID NO: 91 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 91 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 91 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 91 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(oo) the amino acid sequence of SEQ ID NO: 92, wherein X at position 169 of SEQ ID NO: 92 is Ser or Cys;

(pp) both (nn) and (oo);

(qq) the amino acid sequence of SEQ ID NO: 93;

(rr) the amino acid sequence of SEQ ID NO: 94;

(ss) the amino acid sequence of SEQ ID NO: 95;

(tt) the amino acid sequence of SEQ ID NO: 96;

(uu) both (qq) and (rr);

(vv) both (ss) and (tt);

(ww) the amino acid sequence of SEQ ID NO: 97, wherein:

(i) X at position 178 of SEQ ID NO: 97 is Thr or Cys;

(ii) X at position 242 of SEQ ID NO: 97 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 244 of SEQ ID NO: 97 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 245 of SEQ ID NO: 97 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(xx) the amino acid sequence of SEQ ID NO: 98, wherein X at position 188 of SEQ ID NO: 98 is Ser or Cys;

(yy) both (ww) and (xx);

(zz) the amino acid sequence of SEQ ID NO: 99, wherein:

(i) X at position 157 of SEQ ID NO: 99 is Thr or Cys;

(ii) X at position 221 of SEQ ID NO: 99 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 223 of SEQ ID NO: 99 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 224 of SEQ ID NO: 99 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(aaa) the amino acid sequence of SEQ ID NO: 100, wherein X at position 169 of SEQ ID NO: 100 is Ser or Cys;

(bbb) both (zz) and (aaa);

(ccc) the amino acid sequence of SEQ ID NO: 101;

(ddd) the amino acid sequence of SEQ ID NO: 102;

(eee) the amino acid sequence of SEQ ID NO: 103;

(fff) the amino acid sequence of SEQ ID NO: 104;

(ggg) both (ccc) and (ddd);

(hhh) both (eee) and (fff);

(iii) the amino acid sequence of SEQ ID NO: 189, wherein:

(i) X at position 176 of SEQ ID NO: 189 is Thr or Cys;

(ii) X at position 240 of SEQ ID NO: 189 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 242 of SEQ ID NO: 189 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 243 of SEQ ID NO: 189 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(jjj) the amino acid sequence of SEQ ID NO: 190, wherein X at position 188 of SEQ ID NO: 190 is Ser or Cys;

(kkk) both (iii) and (jjj);

(lll) the amino acid sequence of SEQ ID NO: 191, wherein:

(i) X at position 157 of SEQ ID NO: 191 is Thr or Cys;

(ii) X at position 221 of SEQ ID NO: 191 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 223 of SEQ ID NO: 191 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 224 of SEQ ID NO: 191 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(mmm) the amino acid sequence of SEQ ID NO: 192, wherein X at position 169 of SEQ ID NO: 192 is Ser or Cys;

(nnn) both (lll) and (mmm);

(ooo) the amino acid sequence of SEQ ID NO: 193;

(ppp) the amino acid sequence of SEQ ID NO: 194;

(qqq) the amino acid sequence of SEQ ID NO: 195;

(rrr) the amino acid sequence of SEQ ID NO: 196;

(sss) both (ooo) and (ppp);

(ttt) both (qqq) and (rrr);

(uuu) the amino acid sequence of SEQ ID NO: 197, wherein:

(i) X at position 181 of SEQ ID NO: 197 is Thr or Cys;

(ii) X at position 245 of SEQ ID NO: 197 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 247 of SEQ ID NO: 197 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 248 of SEQ ID NO: 197 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(vvv) the amino acid sequence of SEQ ID NO: 198, wherein X at position 188 of SEQ ID NO: 198 is Ser or Cys;

(www) both (uuu) and (vvv);

(xxx) the amino acid sequence of SEQ ID NO: 199, wherein:

(i) X at position 161 of SEQ ID NO: 199 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 199 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 199 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 199 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(yyy) the amino acid sequence of SEQ ID NO: 200, wherein X at position 169 of SEQ ID NO: 200 is Ser or Cys;

(zzz) both (xxx) and (yyy);

(aaaa) the amino acid sequence of SEQ ID NO: 201;

(bbbb) the amino acid sequence of SEQ ID NO: 202;

(cccc) the amino acid sequence of SEQ ID NO: 203;

(dddd) the amino acid sequence of SEQ ID NO: 204;

(eeee) both (aaaa) and (bbbb);

(ffff) both (cccc) and (dddd);

(gggg) the amino acid sequence of SEQ ID NO: 205, wherein:

(i) X at position 184 of SEQ ID NO: 205 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 205 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 205 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 205 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(hhhh) the amino acid sequence of SEQ ID NO: 206, wherein X at position 190 of SEQ ID NO: 206 is Ser or Cys;

(iiii) both (gggg) and (hhhh);

(jjjj) the amino acid sequence of SEQ ID NO: 207, wherein:

(i) X at position 163 of SEQ ID NO: 207 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 207 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 207 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 207 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(kkkk) the amino acid sequence of SEQ ID NO: 208, wherein X at position 164 of SEQ ID NO: 208 is Ser or Cys;

(llll) both (jjjj) and (kkkk);

(mmmm) the amino acid sequence of SEQ ID NO: 209;

(nnnn) the amino acid sequence of SEQ ID NO: 210;

(oooo) the amino acid sequence of SEQ ID NO: 211;

(pppp) the amino acid sequence of SEQ ID NO: 212;

(qqqq) both (mmmm) and (nnnn);

(rrrr) both (oooo) and (pppp);

(ssss) the amino acid sequence of SEQ ID NO: 213, wherein:

(i) X at position 183 of SEQ ID NO: 213 is Thr or Cys;

(ii) X at position 247 of SEQ ID NO: 213 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 249 of SEQ ID NO: 213 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 250 of SEQ ID NO: 213 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(tttt) the amino acid sequence of SEQ ID NO: 214, wherein X at position 188 of SEQ ID NO: 214 is Ser or Cys;

(uuuu) both (ssss) and (tttt);

(vvvv) the amino acid sequence of SEQ ID NO: 215, wherein:

(i) X at position 161 of SEQ ID NO: 215 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 215 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 215 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 215 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(www) the amino acid sequence of SEQ ID NO: 216, wherein X at position 169 of SEQ ID NO: 216 is Ser or Cys;

(xxxx) both (vvvv) and (www);

(yyyy) the amino acid sequence of SEQ ID NO: 217;

(zzzz) the amino acid sequence of SEQ ID NO: 218;

(aaaaa) the amino acid sequence of SEQ ID NO: 219;

(bbbbb) the amino acid sequence of SEQ ID NO: 220;

(ccccc) both (yyyy) and (zzzz);

(ddddd) both (aaaaa) and (bbbbb);

(eeee) the amino acid sequence of SEQ ID NO: 221, wherein:

(i) X at position 180 of SEQ ID NO: 221 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 221 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 221 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ffff) the amino acid sequence of SEQ ID NO: 222, wherein X at position 188 of SEQ ID NO: 222 is Ser or Cys;

(ggggg) both (eeee) and (ffff);

(hhhhh) the amino acid sequence of SEQ ID NO: 223, wherein:

(i) X at position 158 of SEQ ID NO: 223 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 223 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 223 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iiii) the amino acid sequence of SEQ ID NO: 224, wherein X at position 169 of SEQ ID NO: 224 is Ser or Cys;

(jjjjj) both (hhhhh) and (iiii);

(kkkkk) the amino acid sequence of SEQ ID NO: 225;

(lllll) the amino acid sequence of SEQ ID NO: 226;

(mmmmm) the amino acid sequence of SEQ ID NO: 227;

(nnnnn) the amino acid sequence of SEQ ID NO: 228;

(ooooo) both (kkkkk) and (lllll);

(ppppp) both (mmmmm) and (nnnnn);

(qqqqq) the amino acid sequence of SEQ ID NO: 229, wherein:

(i) X at position 184 of SEQ ID NO: 229 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 229 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(rrrrr) the amino acid sequence of SEQ ID NO: 230, wherein X at position 189 of SEQ ID NO: 230 is Ser or Cys;

(sssss) both (qqqqq) and (rrrrr);

(ttttt) the amino acid sequence of SEQ ID NO: 231, wherein:

(i) X at position 163 of SEQ ID NO: 231 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 231 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 231 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(uuuuu) the amino acid sequence of SEQ ID NO: 232, wherein X at position 170 of SEQ ID NO: 232 is Ser or Cys;

(vvvvv) both (ttttt) and (uuuuu);

(wwwww) the amino acid sequence of SEQ ID NO: 233;

(xxxxx) the amino acid sequence of SEQ ID NO: 234;

(yyyyy) the amino acid sequence of SEQ ID NO: 235;

(zzzzz) the amino acid sequence of SEQ ID NO: 236;

(aaaaaa) both (wwwww) and (xxxxx);

(bbbbbb) both (yyyyy) and (zzzzz);

(ccccc) the amino acid sequence of SEQ ID NO: 237, wherein:

(i) X at position 184 of SEQ ID NO: 237 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 237 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 237 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 237 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ddddd) the amino acid sequence of SEQ ID NO: 238, wherein X at position 189 of SEQ ID NO: 238 is Ser or Cys;

(eeeeee) both (ccccc) and (ddddd);

(ffffff) the amino acid sequence of SEQ ID NO: 239, wherein:

(i) X at position 163 of SEQ ID NO: 239 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 239 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 239 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(gggggg) the amino acid sequence of SEQ ID NO: 240, wherein X at position 170 of SEQ ID NO: 240 is Ser or Cys;

(hhhhhh) both (ffffff) and (gggggg);

(iiiiii) the amino acid sequence of SEQ ID NO: 241;
(jjjjjj) the amino acid sequence of SEQ ID NO: 242;
(kkkkkk) the amino acid sequence of SEQ ID NO: 243;
(llllll) the amino acid sequence of SEQ ID NO: 244;
(mmmmmm) both (iiiiii) and (jjjjjj); or
(nnnnnn) both (kkkkkk) and (llllll).

12. An isolated or purified polypeptide comprising a functional portion of the TCR of any one of claims 1-11, 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,
- (c) all of SEQ ID NOs: 1-6,
- (d) all of SEQ ID NOs: 11-13,
- (e) all of SEQ ID NOs: 14-16,
- (f) all of SEQ ID NOs: 11-16,
- (g) all of SEQ ID NOs: 21-23,
- (h) all of SEQ ID NOs: 24-26,
- (i) all of SEQ ID NOs: 21-26,
- (j) all of SEQ ID NOs: 31-33,
- (k) all of SEQ ID NOs: 34-36,
- (l) all of SEQ ID NOs: 31-36,
- (m) all of SEQ ID NOs: 41-43,
- (n) all of SEQ ID NOs: 44-46,
- (o) all of SEQ ID NOs: 41-46
- (p) all of SEQ ID NOs: 119-121,
- (q) all of SEQ ID NOs: 122-124,
- (r) all of SEQ ID NOs: 119-124,
- (s) all of SEQ ID NOs: 129-131,
- (t) all of SEQ ID NOs: 132-134,
- (u) all of SEQ ID NOs: 129-134,
- (v) all of SEQ ID NOs: 139-141,
- (w) all of SEQ ID NOs: 142-144,

- (x) all of SEQ ID NOs: 139-144,
- (y) all of SEQ ID NOs: 149-151,
- (z) all of SEQ ID NOs: 152-154,
- (aa) all of SEQ ID NOs: 149-154,
- (bb) all of SEQ ID NOs: 159-161,
- (cc) all of SEQ ID NOs: 162-164,
- (dd) all of SEQ ID NOs: 159-164,
- (ee) all of SEQ ID NOs: 169-171,
- (ff) all of SEQ ID NOs: 172-174,
- (gg) all of SEQ ID NOs: 169-174,
- (hh) all of SEQ ID NOs: 179-181,
- (ii) all of SEQ ID NOs: 182-184, or
- (jj) all of SEQ ID NOs: 179-184.

13. The isolated or purified polypeptide according to claim 12, wherein the functional portion comprises the amino acid sequence(s) of:

- (1) SEQ ID NO: 7,
- (2) SEQ ID NO: 8,
- (3) SEQ ID NO: 9,
- (4) SEQ ID NO: 10,
- (5) SEQ ID NO: 17,
- (6) SEQ ID NO: 18,
- (7) SEQ ID NO: 19,
- (8) SEQ ID NO: 20,
- (9) SEQ ID NO: 27,
- (10) SEQ ID NO: 28,
- (11) SEQ ID NO: 29,
- (12) SEQ ID NO: 30,
- (13) SEQ ID NO: 37,
- (14) SEQ ID NO: 38,
- (15) SEQ ID NO: 39,
- (16) SEQ ID NO: 40,
- (17) SEQ ID NO: 47,

- (18) SEQ ID NO: 48,
- (19) SEQ ID NO: 49,
- (20) SEQ ID NO: 50,
- (21) SEQ ID NO: 125,
- (22) SEQ ID NO: 126,
- (23) SEQ ID NO: 127,
- (24) SEQ ID NO: 128,
- (25) SEQ ID NO: 135,
- (26) SEQ ID NO: 136,
- (27) SEQ ID NO: 137,
- (28) SEQ ID NO: 138,
- (29) SEQ ID NO: 145,
- (30) SEQ ID NO: 146,
- (31) SEQ ID NO: 147,
- (32) SEQ ID NO: 148,
- (33) SEQ ID NO: 155,
- (34) SEQ ID NO: 156,
- (35) SEQ ID NO: 157,
- (36) SEQ ID NO: 158,
- (37) SEQ ID NO: 165,
- (38) SEQ ID NO: 166,
- (39) SEQ ID NO: 167,
- (40) SEQ ID NO: 168,
- (41) SEQ ID NO: 175,
- (42) SEQ ID NO: 176,
- (43) SEQ ID NO: 177,
- (44) SEQ ID NO: 178,
- (45) SEQ ID NO: 185,
- (46) SEQ ID NO: 186,
- (47) SEQ ID NO: 187,
- (48) SEQ ID NO: 188,
- (49) both of SEQ ID NOs: 7 and 8,
- (50) both of SEQ ID NOs: 9 and 10,

- (51) both of SEQ ID NOs: 17 and 18,
- (52) both of SEQ ID NOs: 19 and 20,
- (53) both of SEQ ID NOs: 27 and 28,
- (54) both of SEQ ID NOs: 29 and 30,
- (55) both of SEQ ID NOs: 37 and 38,
- (56) both of SEQ ID NOs: 39 and 40,
- (57) both of SEQ ID NOs: 47 and 48,
- (58) both of SEQ ID NOs: 49 and 50,
- (59) both of SEQ ID NOs: 125 and 126,
- (60) both of SEQ ID NOs: 127 and 128,
- (61) both of SEQ ID NOs: 135 and 136,
- (62) both of SEQ ID NOs: 137 and 138,
- (63) both of SEQ ID NOs: 145 and 146,
- (64) both of SEQ ID NOs: 147 and 148,
- (65) both of SEQ ID NOs: 155 and 156,
- (66) both of SEQ ID NOs: 157 and 158,
- (67) both of SEQ ID NOs: 165 and 166,
- (68) both of SEQ ID NOs: 167 and 168,
- (69) both of SEQ ID NOs: 175 and 176,
- (70) both of SEQ ID NOs: 177 and 178,
- (71) both of SEQ ID NOs: 185 and 186, or
- (72) both of SEQ ID NOs: 187 and 188.

14. The isolated or purified polypeptide of claim 12 or 13, further comprising:

(a) the amino acid sequence of SEQ ID NO: 59, wherein:

(i) X at position 48 of SEQ ID NO: 59 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 59 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 59 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 59 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 60, wherein X at position 57 of SEQ ID NO: 60 is Ser or Cys; or

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

15. The isolated or purified polypeptide of any one of claims 12-14, comprising:

(a) the amino acid sequence of SEQ ID NO: 65, wherein:

(i) X at position 180 of SEQ ID NO: 65 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 65 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 65 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 65 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(b) the amino acid sequence of SEQ ID NO: 66, wherein X at position 188 of SEQ ID NO: 66 is Ser or Cys;

(c) both (a) and (b);

(d) the amino acid sequence of SEQ ID NO: 67, wherein:

(i) X at position 158 of SEQ ID NO: 67 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 67 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 67 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 67 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(e) the amino acid sequence of SEQ ID NO: 68, wherein X at position 169 of SEQ ID NO: 68 is Ser or Cys;

(f) both (d) and (e);

(g) the amino acid sequence of SEQ ID NO: 69;

(h) the amino acid sequence of SEQ ID NO: 70;

(i) the amino acid sequence of SEQ ID NO: 71;

(j) the amino acid sequence of SEQ ID NO: 72;

(k) both (g) and (h);

(l) both (i) and (j);

(m) the amino acid sequence of SEQ ID NO: 73, wherein:

- (i) X at position 180 of SEQ ID NO: 73 is Thr or Cys;
- (ii) X at position 244 of SEQ ID NO: 73 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 246 of SEQ ID NO: 73 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 247 of SEQ ID NO: 73 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(n) the amino acid sequence of SEQ ID NO: 74, wherein X at position 188 of SEQ ID NO: 74 is Ser or Cys;

(o) both (m) and (n);

(p) the amino acid sequence of SEQ ID NO: 75, wherein:

- (i) X at position 158 of SEQ ID NO: 75 is Thr or Cys;
- (ii) X at position 222 of SEQ ID NO: 75 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 224 of SEQ ID NO: 75 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 225 of SEQ ID NO: 75 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(q) the amino acid sequence of SEQ ID NO: 76, wherein X at position 169 of SEQ ID NO: 76 is Ser or Cys;

(r) both (p) and (q);

(s) the amino acid sequence of SEQ ID NO: 77;

(t) the amino acid sequence of SEQ ID NO: 78;

(u) the amino acid sequence of SEQ ID NO: 79;

(v) the amino acid sequence of SEQ ID NO: 80;

(w) both (s) and (t);

(x) both (u) and (v);

(y) the amino acid sequence of SEQ ID NO: 81, wherein:

- (i) X at position 177 of SEQ ID NO: 81 is Thr or Cys;
- (ii) X at position 241 of SEQ ID NO: 81 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 243 of SEQ ID NO: 81 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 244 of SEQ ID NO: 81 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(z) the amino acid sequence of SEQ ID NO: 82, wherein X at position 189 of SEQ ID NO: 82 is Ser or Cys;

(aa) both (y) and (z);

(bb) the amino acid sequence of SEQ ID NO: 83, wherein:

(i) X at position 160 of SEQ ID NO: 83 is Thr or Cys;

(ii) X at position 224 of SEQ ID NO: 83 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 226 of SEQ ID NO: 83 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 227 of SEQ ID NO: 83 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(cc) the amino acid sequence of SEQ ID NO: 84, wherein X at position 170 of SEQ ID NO: 84 is Ser or Cys;

(dd) both (bb) and (cc);

(ee) the amino acid sequence of SEQ ID NO: 85;

(ff) the amino acid sequence of SEQ ID NO: 86;

(gg) the amino acid sequence of SEQ ID NO: 87;

(hh) the amino acid sequence of SEQ ID NO: 88;

(ii) both (ee) and (ff);

(jj) both (gg) and (hh);

(kk) the amino acid sequence of SEQ ID NO: 89, wherein:

(i) X at position 183 of SEQ ID NO: 89 is Thr or Cys;

(ii) X at position 247 of SEQ ID NO: 89 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 249 of SEQ ID NO: 89 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 250 of SEQ ID NO: 89 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ll) the amino acid sequence of SEQ ID NO: 90, wherein X at position 188 of SEQ ID NO: 90 is Ser or Cys;

(mm) both (kk) and (ll);

(nn) the amino acid sequence of SEQ ID NO: 91, wherein:

(i) X at position 161 of SEQ ID NO: 91 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 91 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 91 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 91 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(oo) the amino acid sequence of SEQ ID NO: 92, wherein X at position 169 of SEQ ID NO: 92 is Ser or Cys;

(pp) both (nn) and (oo);

(qq) the amino acid sequence of SEQ ID NO: 93;

(rr) the amino acid sequence of SEQ ID NO: 94;

(ss) the amino acid sequence of SEQ ID NO: 95;

(tt) the amino acid sequence of SEQ ID NO: 96;

(uu) both (qq) and (rr);

(vv) both (ss) and (tt);

(ww) the amino acid sequence of SEQ ID NO: 97, wherein:

(i) X at position 178 of SEQ ID NO: 97 is Thr or Cys;

(ii) X at position 242 of SEQ ID NO: 97 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 244 of SEQ ID NO: 97 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 245 of SEQ ID NO: 97 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(xx) the amino acid sequence of SEQ ID NO: 98, wherein X at position 188 of SEQ ID NO: 98 is Ser or Cys;

(yy) both (ww) and (xx);

(zz) the amino acid sequence of SEQ ID NO: 99, wherein:

(i) X at position 157 of SEQ ID NO: 99 is Thr or Cys;

(ii) X at position 221 of SEQ ID NO: 99 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 223 of SEQ ID NO: 99 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 224 of SEQ ID NO: 99 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(aaa) the amino acid sequence of SEQ ID NO: 100, wherein X at position 169 of SEQ ID NO: 100 is Ser or Cys;

(bbb) both (zz) and (aaa);

(ccc) the amino acid sequence of SEQ ID NO: 101;

(ddd) the amino acid sequence of SEQ ID NO: 102;

(eee) the amino acid sequence of SEQ ID NO: 103;

(fff) the amino acid sequence of SEQ ID NO: 104;

(ggg) both (ccc) and (ddd);

(hhh) both (eee) and (fff);

(iii) the amino acid sequence of SEQ ID NO: 189, wherein:

(i) X at position 176 of SEQ ID NO: 189 is Thr or Cys;

(ii) X at position 240 of SEQ ID NO: 189 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 242 of SEQ ID NO: 189 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 243 of SEQ ID NO: 189 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(jjj) the amino acid sequence of SEQ ID NO: 190, wherein X at position 188 of SEQ ID NO: 190 is Ser or Cys;

(kkk) both (iii) and (jjj);

(lll) the amino acid sequence of SEQ ID NO: 191, wherein:

(i) X at position 157 of SEQ ID NO: 191 is Thr or Cys;

(ii) X at position 221 of SEQ ID NO: 191 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 223 of SEQ ID NO: 191 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 224 of SEQ ID NO: 191 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(mmm) the amino acid sequence of SEQ ID NO: 192, wherein X at position 169 of SEQ ID NO: 192 is Ser or Cys;

(nnn) both (lll) and (mmm);

(ooo) the amino acid sequence of SEQ ID NO: 193;

(ppp) the amino acid sequence of SEQ ID NO: 194;

(qqq) the amino acid sequence of SEQ ID NO: 195;

(rrr) the amino acid sequence of SEQ ID NO: 196;

(sss) both (ooo) and (ppp);

(ttt) both (qqq) and (rrr);

(uuu) the amino acid sequence of SEQ ID NO: 197, wherein:

(i) X at position 181 of SEQ ID NO: 197 is Thr or Cys;

(ii) X at position 245 of SEQ ID NO: 197 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 247 of SEQ ID NO: 197 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 248 of SEQ ID NO: 197 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(vvv) the amino acid sequence of SEQ ID NO: 198, wherein X at position 188 of SEQ ID NO: 198 is Ser or Cys;

(www) both (uuu) and (vvv);

(xxx) the amino acid sequence of SEQ ID NO: 199, wherein:

(i) X at position 161 of SEQ ID NO: 199 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 199 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 199 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 199 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(yyy) the amino acid sequence of SEQ ID NO: 200, wherein X at position 169 of SEQ ID NO: 200 is Ser or Cys;

(zzz) both (xxx) and (yyy);

(aaaa) the amino acid sequence of SEQ ID NO: 201;

(bbbb) the amino acid sequence of SEQ ID NO: 202;

(cccc) the amino acid sequence of SEQ ID NO: 203;

(dddd) the amino acid sequence of SEQ ID NO: 204;

(eeee) both (aaaa) and (bbbb);

(ffff) both (cccc) and (dddd);

(gggg) the amino acid sequence of SEQ ID NO: 205, wherein:

(i) X at position 184 of SEQ ID NO: 205 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 205 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 205 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 205 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(hhhh) the amino acid sequence of SEQ ID NO: 206, wherein X at position 190 of SEQ ID NO: 206 is Ser or Cys;

(iiii) both (gggg) and (hhhh);

(jjjj) the amino acid sequence of SEQ ID NO: 207, wherein:

(i) X at position 163 of SEQ ID NO: 207 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 207 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 207 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 207 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(kkkk) the amino acid sequence of SEQ ID NO: 208, wherein X at position 164 of SEQ ID NO: 208 is Ser or Cys;

(llll) both (jjjj) and (kkkk);

(mmmm) the amino acid sequence of SEQ ID NO: 209;

(nnnn) the amino acid sequence of SEQ ID NO: 210;

(oooo) the amino acid sequence of SEQ ID NO: 211;

(pppp) the amino acid sequence of SEQ ID NO: 212;

(qqqq) both (mmmm) and (nnnn);

(rrrr) both (oooo) and (pppp);

(ssss) the amino acid sequence of SEQ ID NO: 213, wherein:

(i) X at position 183 of SEQ ID NO: 213 is Thr or Cys;

(ii) X at position 247 of SEQ ID NO: 213 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 249 of SEQ ID NO: 213 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 250 of SEQ ID NO: 213 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(tttt) the amino acid sequence of SEQ ID NO: 214, wherein X at position 188 of SEQ ID NO: 214 is Ser or Cys;

(uuuu) both (ssss) and (tttt);

(vvvv) the amino acid sequence of SEQ ID NO: 215, wherein:

(i) X at position 161 of SEQ ID NO: 215 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 215 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 215 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 215 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(www) the amino acid sequence of SEQ ID NO: 216, wherein X at position 169 of SEQ ID NO: 216 is Ser or Cys;

(xxxx) both (vvvv) and (www);

(yyyy) the amino acid sequence of SEQ ID NO: 217;

(zzzz) the amino acid sequence of SEQ ID NO: 218;

(aaaa) the amino acid sequence of SEQ ID NO: 219;

(bbbb) the amino acid sequence of SEQ ID NO: 220;

(cccc) both (yyyy) and (zzzz);

(dddd) both (aaaa) and (bbbb);

(eeee) the amino acid sequence of SEQ ID NO: 221, wherein:

(i) X at position 180 of SEQ ID NO: 221 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 221 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 221 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(fffff) the amino acid sequence of SEQ ID NO: 222, wherein X at position 188 of SEQ ID NO: 222 is Ser or Cys;

(ggggg) both (eeeeee) and (fffff);

(hhhhh) the amino acid sequence of SEQ ID NO: 223, wherein:

(i) X at position 158 of SEQ ID NO: 223 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 223 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 223 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iiiiii) the amino acid sequence of SEQ ID NO: 224, wherein X at position 169 of SEQ ID NO: 224 is Ser or Cys;

(jjjjj) both (hhhhh) and (iiiiii);

(kkkkk) the amino acid sequence of SEQ ID NO: 225;

(lllll) the amino acid sequence of SEQ ID NO: 226;

(mmmmm) the amino acid sequence of SEQ ID NO: 227;

(nnnnn) the amino acid sequence of SEQ ID NO: 228;

(ooooo) both (kkkkk) and (lllll);

(ppppp) both (mmmmm) and (nnnnn);

(qqqqq) the amino acid sequence of SEQ ID NO: 229, wherein:

(i) X at position 184 of SEQ ID NO: 229 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 229 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(rrrrr) the amino acid sequence of SEQ ID NO: 230, wherein X at position 189 of SEQ ID NO: 230 is Ser or Cys;

(sssss) both (qqqqq) and (rrrrr);

(ttttt) the amino acid sequence of SEQ ID NO: 231, wherein:

(i) X at position 163 of SEQ ID NO: 231 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 231 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 231 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(uuuuu) the amino acid sequence of SEQ ID NO: 232, wherein X at position 170 of SEQ ID NO: 232 is Ser or Cys;

(vvvvv) both (ttttt) and (uuuuu);

(wwwww) the amino acid sequence of SEQ ID NO: 233;

(xxxxx) the amino acid sequence of SEQ ID NO: 234;

(yyyyy) the amino acid sequence of SEQ ID NO: 235;

(zzzzz) the amino acid sequence of SEQ ID NO: 236;

(aaaaa) both (wwwww) and (xxxxx);

(bbbbbb) both (yyyyy) and (zzzzz);

(ccccc) the amino acid sequence of SEQ ID NO: 237, wherein:

(i) X at position 184 of SEQ ID NO: 237 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 237 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 237 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 237 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ddddd) the amino acid sequence of SEQ ID NO: 238, wherein X at position 189 of SEQ ID NO: 238 is Ser or Cys;

(eeeeee) both (ccccc) and (ddddd);

(fffff) the amino acid sequence of SEQ ID NO: 239, wherein:

(i) X at position 163 of SEQ ID NO: 239 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 239 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 239 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(gggggg) the amino acid sequence of SEQ ID NO: 240, wherein X at position 170 of SEQ ID NO: 240 is Ser or Cys;

(hhhhhh) both (ffffff) and (gggggg);

(iiiiii) the amino acid sequence of SEQ ID NO: 241;

(jjjjjj) the amino acid sequence of SEQ ID NO: 242;

(kkkkkk) the amino acid sequence of SEQ ID NO: 243;

(llllll) the amino acid sequence of SEQ ID NO: 244;

(mmmmmm) both (iiiiii) and (jjjjjj); or

(nnnnnn) both (kkkkkk) and (llllll).

16. An isolated or purified protein, comprising:

(a) 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;

(b) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 11-13 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 14-16;

(c) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 21-23 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 24-26;

(d) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 31-33 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 34-36;

(e) a first polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 41-43 and a second polypeptide chain comprising the amino acid sequences of SEQ ID NOs: 44-46

(f) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 119-121 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 122-124,

(g) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 129-131 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 132-134,

(h) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 139-141 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 142-144,

(i) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 149-151 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 152-154,

(j) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 159-161 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 162-164,

(k) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 169-171 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 172-174, or

(l) a first polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 179-181 and a second polypeptide chain comprising the amino acid sequences of all of SEQ ID NOs: 182-184.

17. The isolated or purified protein according to claim 16, wherein:

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 7 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 8;

(ii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 9 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 10;

(iii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 17 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 18;

(iv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 19 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 20;

(v) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 27 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 28;

(vi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 29 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 30;

(vii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 37 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 38;

(viii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 39 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 40;

(ix) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 47 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 48;

(x) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 49 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 50;

(xi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 125 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 126;

(xii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 127 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 128;

(xiii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 135 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 136;

(xiv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 137 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 138;

(xv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 145 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 146;

(xvi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 147 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 148;

(xvii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 155 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 156;

(xviii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 157 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 158;

(xix) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 165 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 166;

(xx) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 167 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 168;

(xxi) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 175 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 176;

(xxii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 177 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 178;

(xxiii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 185 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 186; or

(xxiv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 187 and the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 188.

18. The isolated or purified protein of claim 16 or 17, wherein:

(a) the first polypeptide chain further comprises the amino acid sequence of SEQ ID NO: 59, wherein:

(i) X at position 48 of SEQ ID NO: 59 is Thr or Cys;

(ii) X at position 112 of SEQ ID NO: 59 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 114 of SEQ ID NO: 59 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 115 of SEQ ID NO: 59 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: 60, wherein X at position 57 of SEQ ID NO: 60 is Ser or Cys; or

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

19. The isolated or purified protein of any one of claims 16-18, wherein:

(a) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 65, wherein:

(i) X at position 180 of SEQ ID NO: 65 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 65 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 65 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 65 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: 66, wherein X at position 188 of SEQ ID NO: 66 is Ser or Cys;

(c) both (a) and (b);

(d) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 67, wherein:

(i) X at position 158 of SEQ ID NO: 67 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 67 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 67 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 67 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(e) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 68, wherein X at position 169 of SEQ ID NO: 68 is Ser or Cys;

(f) both (d) and (e);

(g) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 69;

(h) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 70;

(i) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 71;

- (j) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 72;
- (k) both (g) and (h);
- (l) both (i) and (j);
- (m) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 73, wherein:
- (i) X at position 180 of SEQ ID NO: 73 is Thr or Cys;
- (ii) X at position 244 of SEQ ID NO: 73 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 246 of SEQ ID NO: 73 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 247 of SEQ ID NO: 73 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (n) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 74, wherein X at position 188 of SEQ ID NO: 74 is Ser or Cys;
- (o) both (m) and (n);
- (p) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 75, wherein:
- (i) X at position 158 of SEQ ID NO: 75 is Thr or Cys;
- (ii) X at position 222 of SEQ ID NO: 75 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 224 of SEQ ID NO: 75 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 225 of SEQ ID NO: 75 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (q) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 76, wherein X at position 169 of SEQ ID NO: 76 is Ser or Cys;
- (r) both (p) and (q);
- (s) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 77;
- (t) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 78;
- (u) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 79;

- (v) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 80;
- (w) both (s) and (t);
- (x) both (u) and (v);
- (y) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 81, wherein:
- (i) X at position 177 of SEQ ID NO: 81 is Thr or Cys;
- (ii) X at position 241 of SEQ ID NO: 81 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 243 of SEQ ID NO: 81 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 244 of SEQ ID NO: 81 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (z) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 82, wherein X at position 189 of SEQ ID NO: 82 is Ser or Cys;
- (aa) both (y) and (z);
- (bb) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 83, wherein:
- (i) X at position 160 of SEQ ID NO: 83 is Thr or Cys;
- (ii) X at position 224 of SEQ ID NO: 83 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 226 of SEQ ID NO: 83 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 227 of SEQ ID NO: 83 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (cc) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 84, wherein X at position 170 of SEQ ID NO: 84 is Ser or Cys;
- (dd) both (bb) and (cc);
- (ee) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 85;
- (ff) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 86;

- (gg) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 87;
- (hh) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 88;
- (ii) both (ee) and (ff);
- (jj) both (gg) and (hh);
- (kk) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 89, wherein:
- (i) X at position 183 of SEQ ID NO: 89 is Thr or Cys;
- (ii) X at position 247 of SEQ ID NO: 89 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 249 of SEQ ID NO: 89 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 250 of SEQ ID NO: 89 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (ll) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 90, wherein X at position 188 of SEQ ID NO: 90 is Ser or Cys;
- (mm) both (kk) and (ll);
- (nn) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 91, wherein:
- (i) X at position 161 of SEQ ID NO: 91 is Thr or Cys;
- (ii) X at position 225 of SEQ ID NO: 91 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 227 of SEQ ID NO: 91 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 228 of SEQ ID NO: 91 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (oo) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 92, wherein X at position 169 of SEQ ID NO: 92 is Ser or Cys;
- (pp) both (nn) and (oo);
- (qq) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 93;

- (rr) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 94;
- (ss) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 95;
- (tt) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 96;
- (uu) both (qq) and (rr);
- (vv) both (ss) and (tt);
- (ww) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 97, wherein:
- (i) X at position 178 of SEQ ID NO: 97 is Thr or Cys;
 - (ii) X at position 242 of SEQ ID NO: 97 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
 - (iii) X at position 244 of SEQ ID NO: 97 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
 - (iv) X at position 245 of SEQ ID NO: 97 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (xx) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 98, wherein X at position 188 of SEQ ID NO: 98 is Ser or Cys;
- (yy) both (ww) and (xx);
- (zz) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 99, wherein:
- (i) X at position 157 of SEQ ID NO: 99 is Thr or Cys;
 - (ii) X at position 221 of SEQ ID NO: 99 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
 - (iii) X at position 223 of SEQ ID NO: 99 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
 - (iv) X at position 224 of SEQ ID NO: 99 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (aaa) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 100, wherein X at position 169 of SEQ ID NO: 100 is Ser or Cys;
- (bbb) both (zz) and (aaa);
- (ccc) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 101;

(ddd) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 102;

(eee) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 103;

(fff) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 104;

(ggg) both (ccc) and (ddd);

(hhh) both (eee) and (fff);

(iii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 189, wherein:

- (i) X at position 176 of SEQ ID NO: 189 is Thr or Cys;
- (ii) X at position 240 of SEQ ID NO: 189 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 242 of SEQ ID NO: 189 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 243 of SEQ ID NO: 189 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(jjj) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 190, wherein X at position 188 of SEQ ID NO: 190 is Ser or Cys;

(kkk) both (iii) and (jjj);

(lll) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 191, wherein:

- (i) X at position 157 of SEQ ID NO: 191 is Thr or Cys;
- (ii) X at position 221 of SEQ ID NO: 191 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 223 of SEQ ID NO: 191 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 224 of SEQ ID NO: 191 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(mmm) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 192, wherein X at position 169 of SEQ ID NO: 192 is Ser or Cys;

(nnn) both (lll) and (mmm);

(ooo) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 193;

(ppp) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 194;

(qqq) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 195;

(rrr) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 196;

(sss) both (ooo) and (ppp);

(ttt) both (qqq) and (rrr);

(uuu) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 197, wherein:

(i) X at position 181 of SEQ ID NO: 197 is Thr or Cys;

(ii) X at position 245 of SEQ ID NO: 197 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 247 of SEQ ID NO: 197 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 248 of SEQ ID NO: 197 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(vvv) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 198, wherein X at position 188 of SEQ ID NO: 198 is Ser or Cys;

(www) both (uuu) and (vvv);

(xxx) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 199, wherein:

(i) X at position 161 of SEQ ID NO: 199 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 199 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 199 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 199 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(yyy) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 200, wherein X at position 169 of SEQ ID NO: 200 is Ser or Cys;

(zzz) both (xxx) and (yyy);

(aaaa) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 201;

(bbbb) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 202;

(cccc) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 203;

(dddd) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 204;

(eeee) both (aaaa) and (bbbb);

(ffff) both (cccc) and (dddd);

(gggg) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 205, wherein:

(i) X at position 184 of SEQ ID NO: 205 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 205 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 205 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 205 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(hhhh) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 206, wherein X at position 190 of SEQ ID NO: 206 is Ser or Cys;

(iiii) both (gggg) and (hhhh);

(jjjj) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 207, wherein:

(i) X at position 163 of SEQ ID NO: 207 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 207 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 207 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 207 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(kkkk) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 208, wherein X at position 164 of SEQ ID NO: 208 is Ser or Cys;

(llll) both (jjjj) and (kkkk);

(mmmm) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 209;

(nnnn) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 210;

(oooo) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 211;

(pppp) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 212;

(qqqq) both (mmmm) and (nnnn);

(rrrr) both (oooo) and (pppp);

(ssss) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 213, wherein:

(i) X at position 183 of SEQ ID NO: 213 is Thr or Cys;

(ii) X at position 247 of SEQ ID NO: 213 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 249 of SEQ ID NO: 213 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 250 of SEQ ID NO: 213 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(tttt) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 214, wherein X at position 188 of SEQ ID NO: 214 is Ser or Cys;

(uuuu) both (ssss) and (tttt);

(vvvv) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 215, wherein:

(i) X at position 161 of SEQ ID NO: 215 is Thr or Cys;

(ii) X at position 225 of SEQ ID NO: 215 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 227 of SEQ ID NO: 215 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 228 of SEQ ID NO: 215 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(www) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 216, wherein X at position 169 of SEQ ID NO: 216 is Ser or Cys;

(xxxx) both (vvvv) and (www);

(yyyy) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 217;

(zzzz) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 218;

(aaaa) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 219;

(bbbb) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 220;

(cccc) both (yyyy) and (zzzz);

(dddd) both (aaaa) and (bbbb);

(eeee) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 221, wherein:

(i) X at position 180 of SEQ ID NO: 221 is Thr or Cys;

(ii) X at position 244 of SEQ ID NO: 221 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 246 of SEQ ID NO: 221 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 247 of SEQ ID NO: 221 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ffff) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 222, wherein X at position 188 of SEQ ID NO: 222 is Ser or Cys;

(gggg) both (eeee) and (ffff);

(hhhh) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 223, wherein:

(i) X at position 158 of SEQ ID NO: 223 is Thr or Cys;

(ii) X at position 222 of SEQ ID NO: 223 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 224 of SEQ ID NO: 223 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 225 of SEQ ID NO: 223 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iiii) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 224, wherein X at position 169 of SEQ ID NO: 224 is Ser or Cys;

(jjjjj) both (hhhhh) and (iiii);

(kkkkk) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 225;

(lllll) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 226;

(mmmmm) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 227;

(nnnnn) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 228;

(ooooo) both (kkkkk) and (lllll);

(ppppp) both (mmmmm) and (nnnnn);

(qqqqq) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 229, wherein:

(i) X at position 184 of SEQ ID NO: 229 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 229 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 229 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 229 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(rrrrr) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 230, wherein X at position 189 of SEQ ID NO: 230 is Ser or Cys;

(sssss) both (qqqqq) and (rrrrr);

(ttttt) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 231, wherein:

(i) X at position 163 of SEQ ID NO: 231 is Thr or Cys;

(ii) X at position 227 of SEQ ID NO: 231 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 229 of SEQ ID NO: 231 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 230 of SEQ ID NO: 231 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(uuuuu) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 232, wherein X at position 170 of SEQ ID NO: 232 is Ser or Cys;

(vvvvv) both (ttttt) and (uuuuu);

(wwwww) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 233;

(xxxxx) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 234;

(yyyyy) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 235;

(zzzzz) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 236;

(aaaaaa) both (wwwww) and (xxxxx);

(bbbbbb) both (yyyyy) and (zzzzz);

(ccccc) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 237, wherein:

(i) X at position 184 of SEQ ID NO: 237 is Thr or Cys;

(ii) X at position 248 of SEQ ID NO: 237 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(iii) X at position 250 of SEQ ID NO: 237 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and

(iv) X at position 251 of SEQ ID NO: 237 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;

(ddddd) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 238, wherein X at position 189 of SEQ ID NO: 238 is Ser or Cys;

(eeeeee) both (ccccc) and (ddddd);

(ffffff) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 239, wherein:

- (i) X at position 163 of SEQ ID NO: 239 is Thr or Cys;
- (ii) X at position 227 of SEQ ID NO: 239 is Ser, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (iii) X at position 229 of SEQ ID NO: 239 is Met, Ala, Val, Leu, Ile, Pro, Phe, or Trp; and
- (iv) X at position 230 of SEQ ID NO: 239 is Gly, Ala, Val, Leu, Ile, Pro, Phe, Met, or Trp;
- (gggggg) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 240, wherein X at position 170 of SEQ ID NO: 240 is Ser or Cys;
- (hhhhhh) both (ffffff) and (gggggg);
- (iiiiii) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 241;
- (jjjjjj) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 242;
- (kkkkkk) the first polypeptide chain comprises the amino acid sequence of SEQ ID NO: 243;
- (llllll) the second polypeptide chain comprises the amino acid sequence of SEQ ID NO: 244;
- (mmmmmm) both (iiiiii) and (jjjjjj); or
- (nnnnnn) both (kkkkkk) and (llllll).

20. An isolated or purified nucleic acid comprising a nucleotide sequence encoding the TCR according to any one of claims 1-11, the polypeptide according to any one of claims 12-15, or the protein according to any one of claims 16-19.

21. 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; 8 and 7; 9 and 10; 10 and 9; 17 and 18; 18 and 17; 19 and 20; 20 and 19; 27 and 28; 28 and 27; 29 and 30; 30 and 29; 37 and 38; 38 and 37; 39 and 40; 40 and 39; 47 and 48; 48 and 47; 49 and 50; 50 and 49; 125 and 126; 126 and 125; 127 and 128; 128 and 127; 135 and 136; 136 and 135; 137 and 138; 138 and 137; 145 and 146; 146 and 145; 147 and 148; 148 and 147; 155 and 156; 156 and 155; 157 and 158; 158 and 157; 165 and 166; 166 and 165; 167 and 168; 168 and

167; 175 and 176; 176 and 175; 177 and 178; 178 and 177; 185 and 186; 186 and 185; 187 and 188; 188 and 187; 65 and 66; 66 and 65; 67 and 68; 68 and 67; 69 and 70; 70 and 69; 71 and 72; 72 and 71; 73 and 74; 74 and 73; 75 and 76; 76 and 75; 77 and 78; 78 and 77; 79 and 80; 80 and 79; 81 and 82; 82 and 81; 83 and 84; 84 and 83; 85 and 86; 86 and 85; 87 and 88; 88 and 87; 89 and 90; 90 and 89; 91 and 92; 92 and 91; 93 and 94; 94 and 93; 95 and 96; 96 and 95; 97 and 98; 98 and 97; 99 and 100; 100 and 99; 101 and 102; 102 and 101; 103 and 104; 104 and 103; 189 and 190; 190 and 189; 191 and 192; 192 and 191; 193 and 194; 194 and 193; 195 and 196; 196 and 195; 197 and 198; 198 and 197; 199 and 200; 200 and 199; 201 and 202; 202 and 201; 203 and 204; 204 and 203; 205 and 206; 206 and 205; 207 and 208; 208 and 207; 209 and 210; 210 and 209; 211 and 212; 212 and 211; 213 and 214; 214 and 213; 215 and 216; 216 and 215; 217 and 218; 218 and 217; 219 and 220; 220 and 219; 221 and 222; 222 and 221; 223 and 224; 224 and 223; 225 and 226; 226 and 225; 227 and 228; 228 and 227; 229 and 230; 230 and 229; 231 and 232; 232 and 231; 233 and 234; 234 and 233; 235 and 236; 236 and 235; 237 and 238; 238 and 237; 239 and 240; 240 and 239; 241 and 242; 242 and 241; 243 and 244; or 244 and 243.

22. The isolated or purified nucleic acid according to claim 21, further comprising a third nucleotide sequence interposed between the first and second nucleotide sequence, wherein the third nucleotide sequence encodes a cleavable linker peptide.

23. The isolated or purified nucleic acid according to claim 22, wherein the cleavable linker peptide comprises the amino acid sequence of RAKRSGSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 105).

24. A recombinant expression vector comprising the nucleic acid according to any one of claims 20-23.

25. The recombinant expression vector according to claim 24, which is a transposon or a lentiviral vector.

26. An isolated or purified TCR, polypeptide, or protein encoded by the nucleic acid according to any one of claims 20-23 or the vector according to claim 24 or 25.

27. An isolated or purified TCR, polypeptide, or protein that results from expression of the nucleic acid according to any one of claims 20-23 or the vector according to claim 24 or 25 in a cell.

28. An *in vitro* method of producing a host cell expressing a TCR that has antigenic specificity for the peptide of MTEYKLVVVGAGDVGKSALTQLIQ (SEQ ID NO: 252), the method comprising contacting a cell with the vector according to claim 24 or 25 under conditions that allow introduction of the vector into the cell.

29. An isolated or purified host cell comprising the nucleic acid according to any one of claims 20-23 or the recombinant expression vector according to claim 24 or 25.

30. The host cell according to claim 29, wherein the cell is a human lymphocyte.

31. The host cell according to claim 29 or 30, wherein the cell is selected from the group consisting of a T cell, a natural killer T (NKT) cell, an invariant natural killer T (iNKT) cell, and a natural killer (NK) cell.

32. An isolated or purified population of cells comprising the host cell according to any one of claims 29-31.

33. A method of producing the TCR according to any one of claims 1-11, 26, or 27, the polypeptide according to any one of claims 12-15, 26, or 27, or the protein according to any one of claims 16-19, 26, or 27, the method comprising culturing the host cell according to any one of claims 29-31, or the population of host cells according to claim 32, so that the TCR, polypeptide, or protein is produced.

34. A pharmaceutical composition comprising (a) the TCR according to any one of claims 1-11, 26, or 27, the polypeptide according to any one of claims 12-15, 26, or 27, the protein according to any one of claims 16-19, 26, or 27, the nucleic acid according to any one of claims 20-23, the recombinant expression vector according to claim 24 or 25, the host cell according to any one of claims 29-31, or the population of cells according to claim 32 and (b) a pharmaceutically acceptable carrier.

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

(a) contacting a sample comprising cells of the cancer with the TCR according to any one of claims 1-11, 26, or 27, the polypeptide according to any one of claims 12-15, 26, or 27, the protein according to any one of claims 16-19, 26, or 27, the nucleic acid according to any one of claims 20-23, the recombinant expression vector according to claim 24 or 25, the host cell according to any one of claims 29-31, the population of cells according to claim 32, or the pharmaceutical composition of claim 34, thereby forming a complex; and

(b) detecting the complex,

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

36. The TCR according to any one of claims 1-11, 26, or 27, the polypeptide according to any one of claims 12-15, 26, or 27, the protein according to any one of claims 16-19, 26, or 27, the nucleic acid according to any one of claims 20-23, the recombinant expression vector according to claim 24 or 25, the host cell according to any one of claims 29-31, the population of cells according to claim 32, or the pharmaceutical composition according to claim 34, for use in the inducement of an immune response against cancer in a mammal.

37. The TCR according to any one of claims 1-11, 26, or 27, the polypeptide according to any one of claims 12-15, 26, or 27, the protein according to any one of claims 16-19, 26, or 27, the nucleic acid according to any one of claims 20-23, the recombinant expression vector according to claim 24 or 25, the host cell according to any one of claims 29-31, the population of cells according to claim 32, or the pharmaceutical composition according to claim 34, for use in the treatment or prevention of cancer in a mammal.

38. The method of claim 35, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of claim 36 or 37, wherein the cancer expresses a mutated human RAS amino acid sequence with a substitution of glycine at position 13 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 13 is defined by reference to the wild-type human KRAS, wild-type human HRAS, or wild-type human NRAS protein, respectively.

39. The method of claim 38, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of claim 38, wherein the mutated human RAS amino acid sequence is a mutated human Kirsten rat sarcoma viral oncogene homolog (KRAS) amino acid sequence.

40. The method of claim 38, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of claim 38, wherein the mutated human RAS amino acid sequence is a mutated human neuroblastoma rat sarcoma viral oncogene homolog (NRAS) amino acid sequence.

41. The method of claim 38, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use of claim 38, wherein the mutated human RAS amino acid sequence is a mutated human Harvey rat sarcoma viral oncogene homolog (HRAS) amino acid sequence.

42. The method of claim 35, or the TCR, polypeptide, protein, nucleic acid, recombinant expression vector, host cell, population of cells, or pharmaceutical composition for the use according to any one of claims 36-41, wherein the cancer is pancreatic, colorectal, lung, endometrial, ovarian, or prostate cancer.

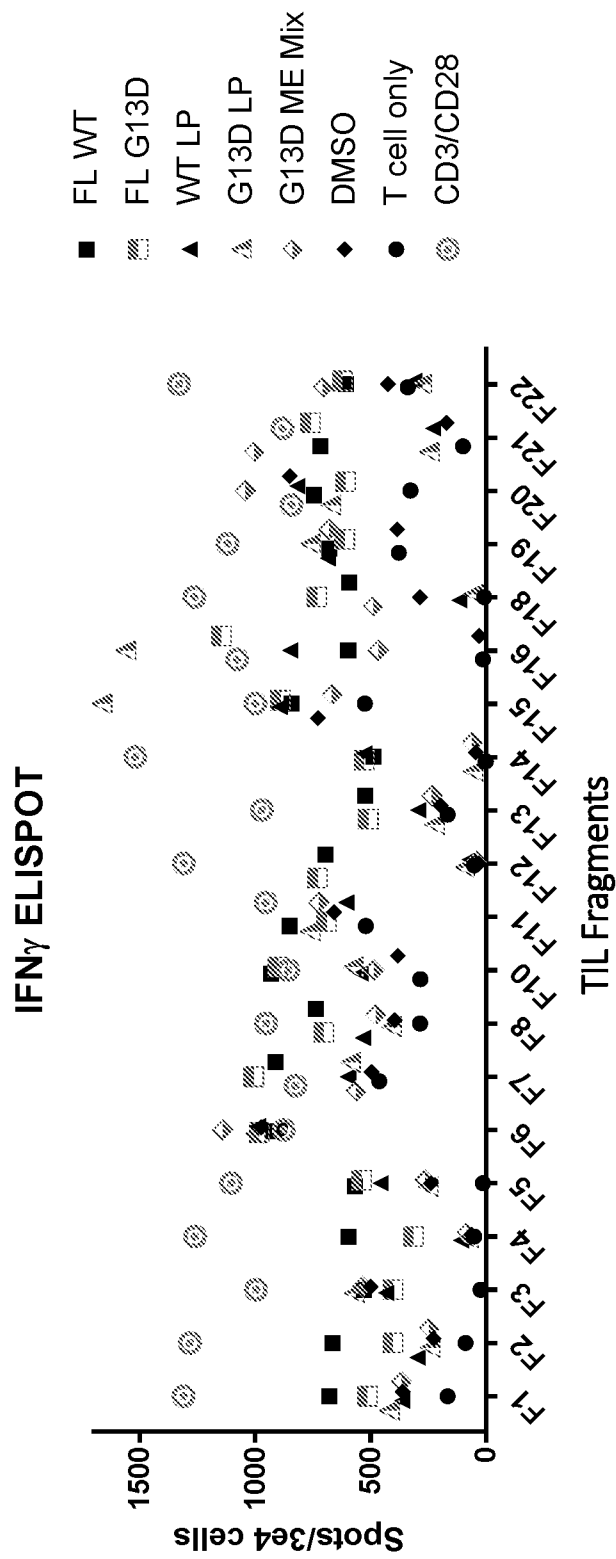


Fig. 1

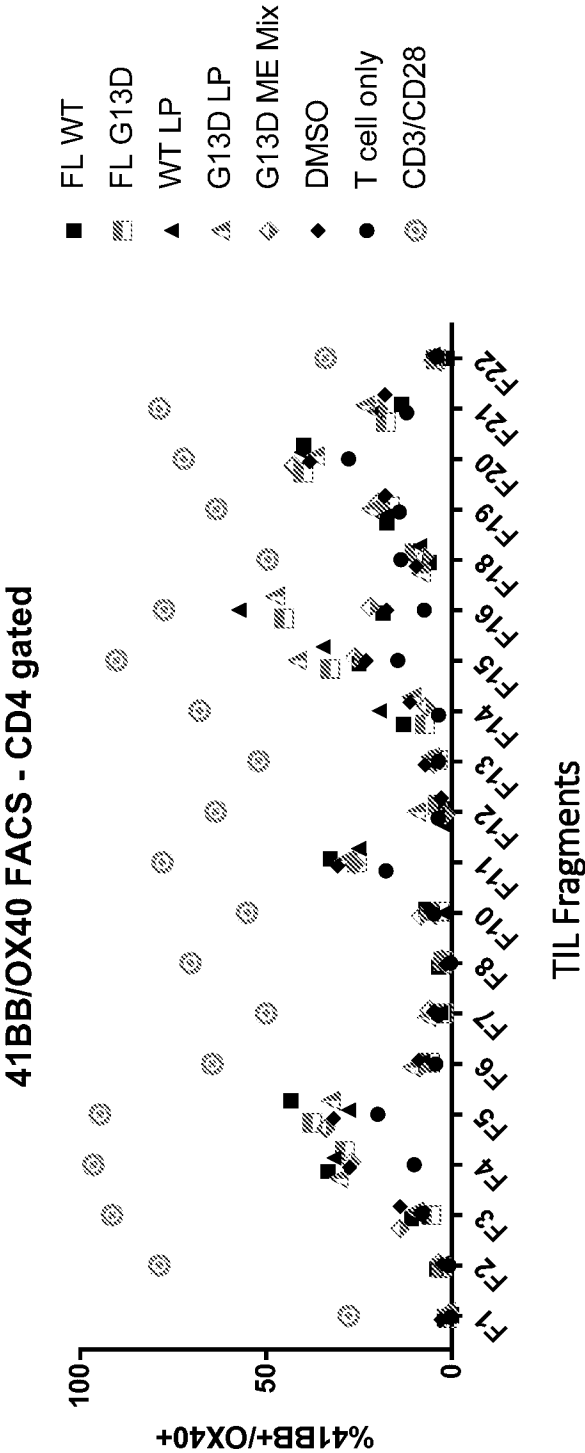


Fig. 2A

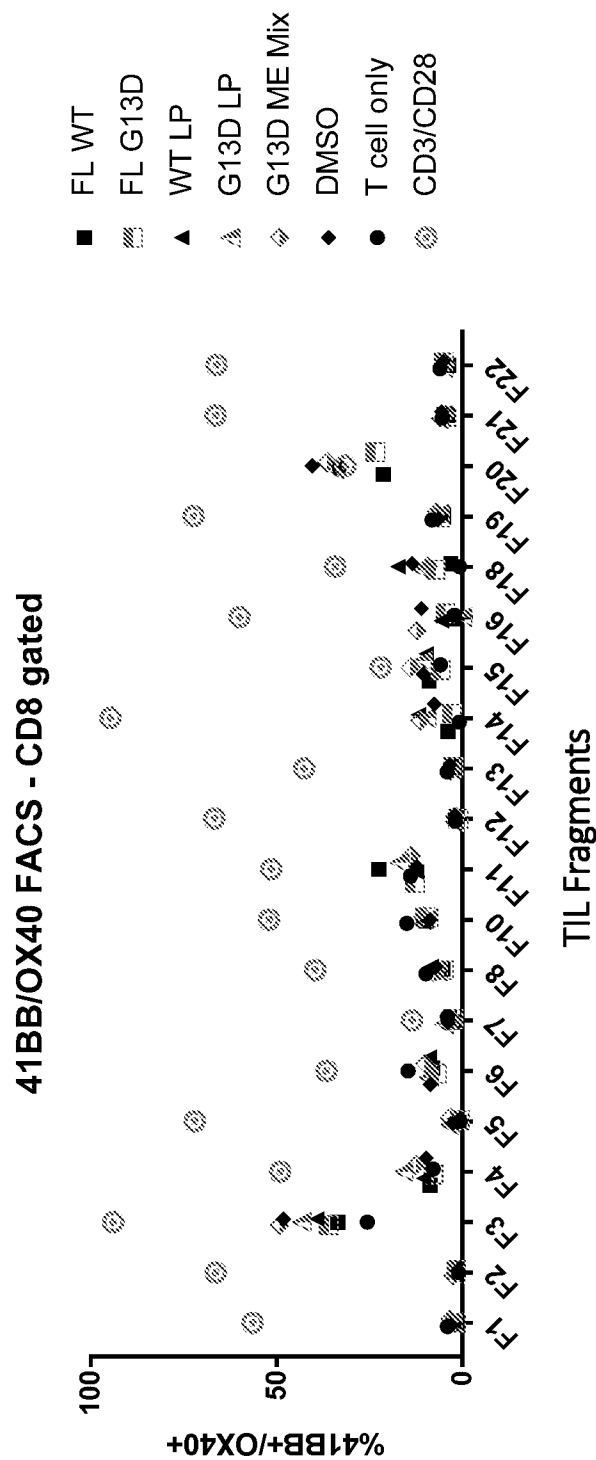


Fig. 2B

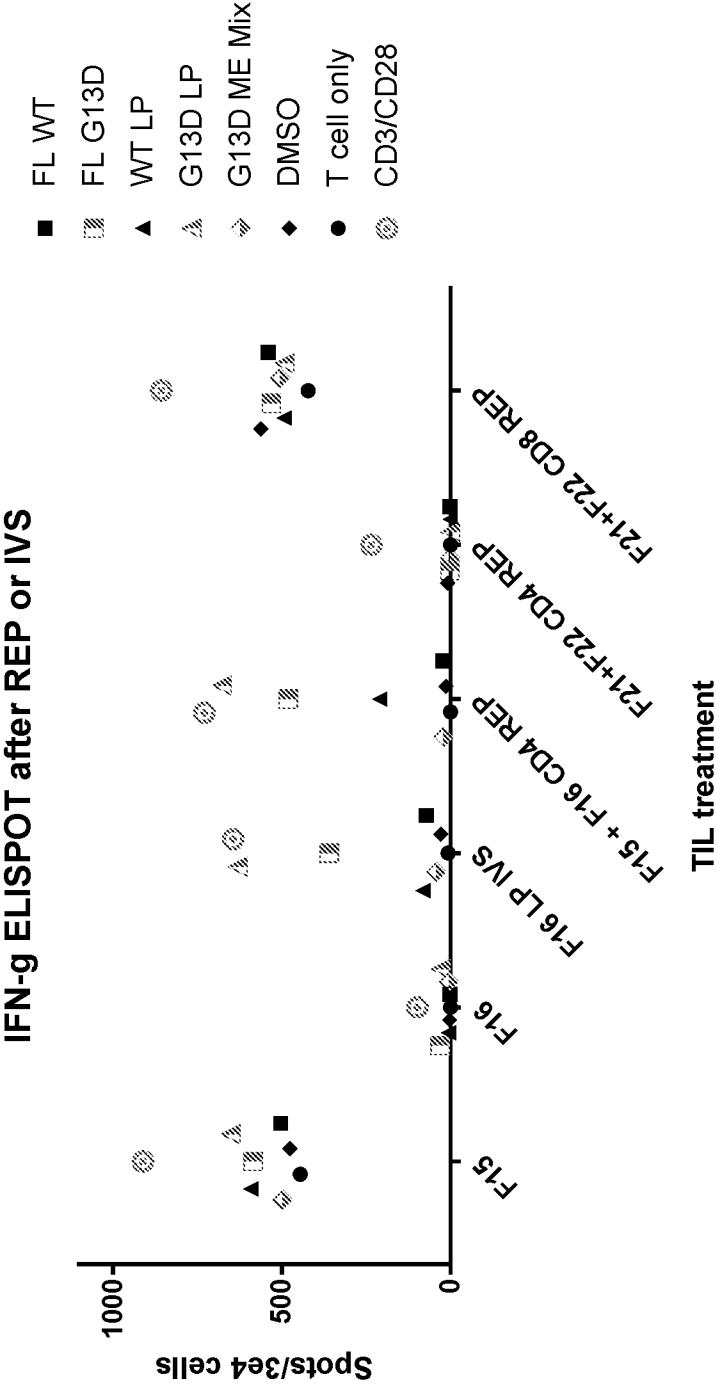


Fig. 3

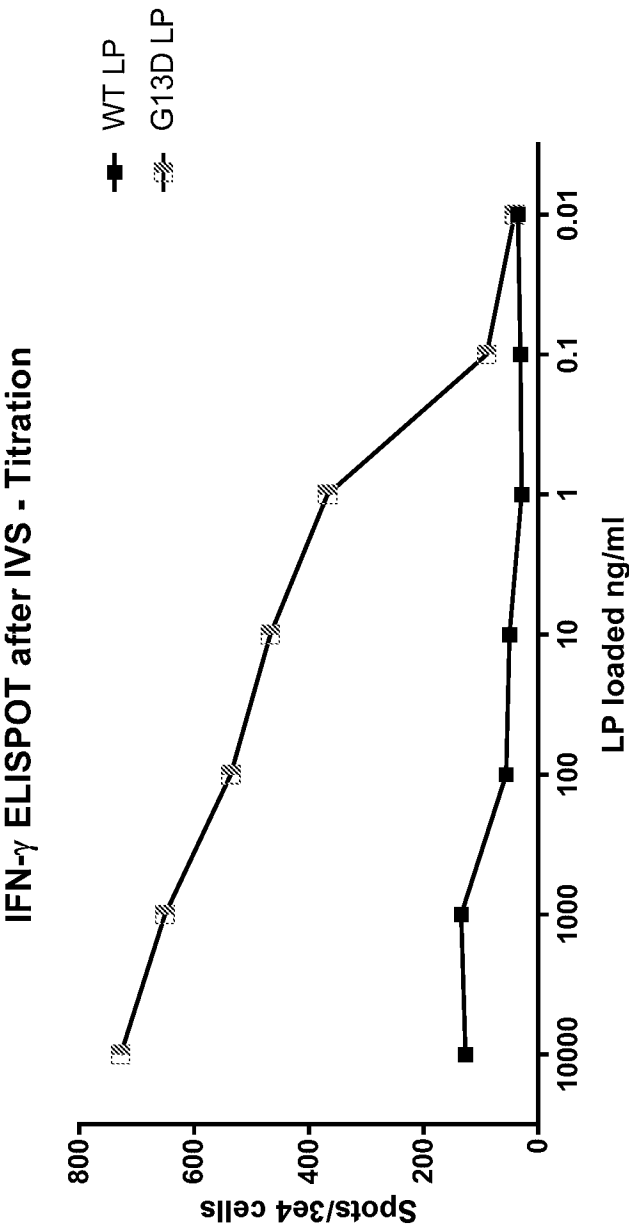


Fig. 4A

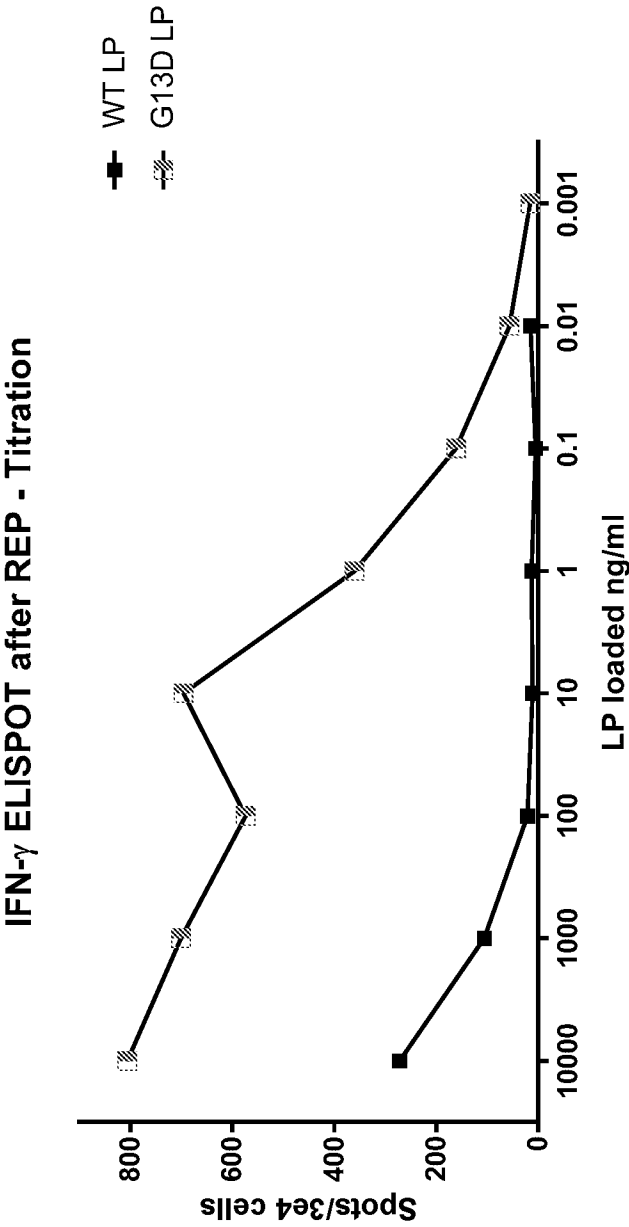


Fig. 4B

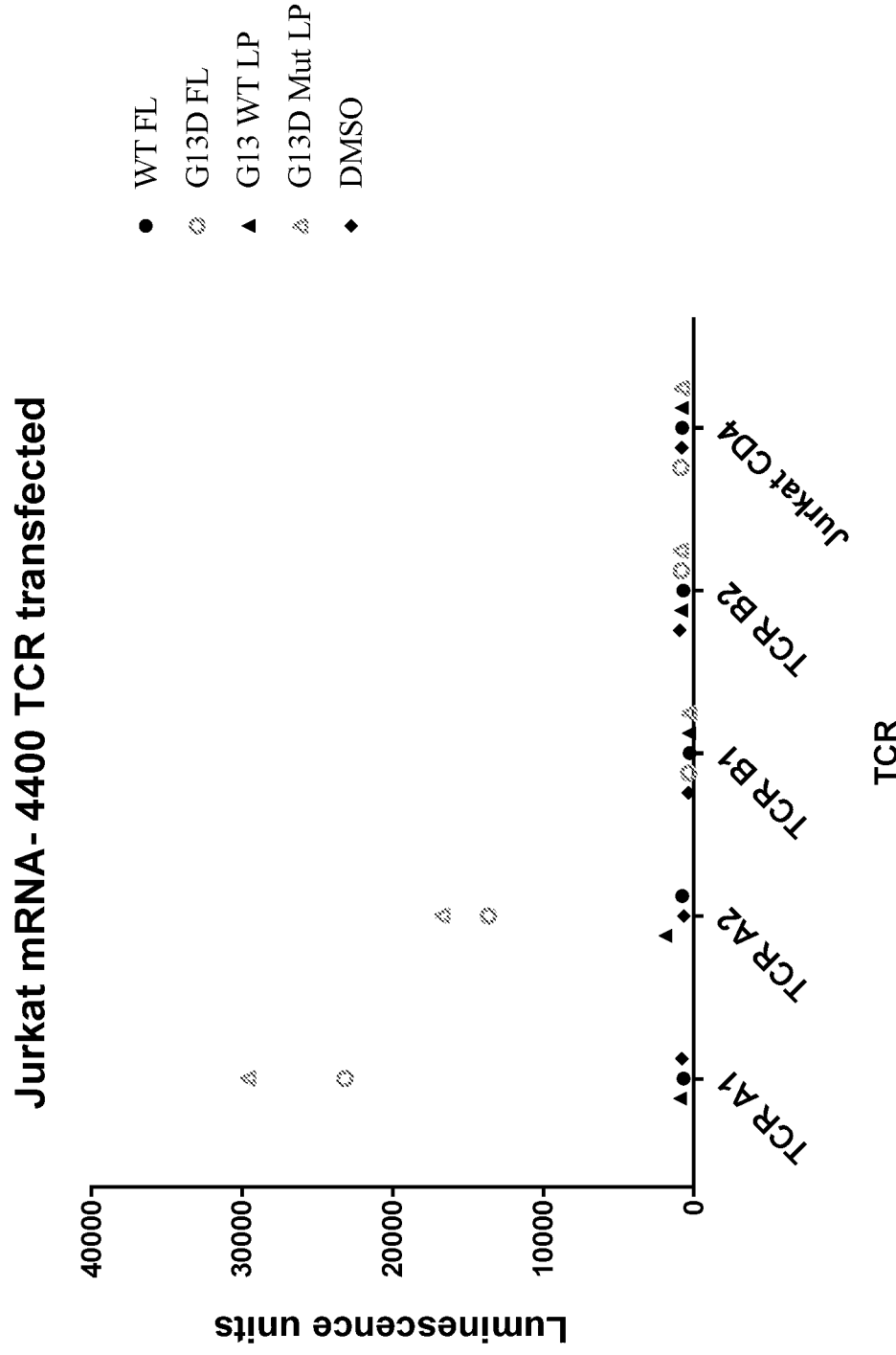


Fig. 5

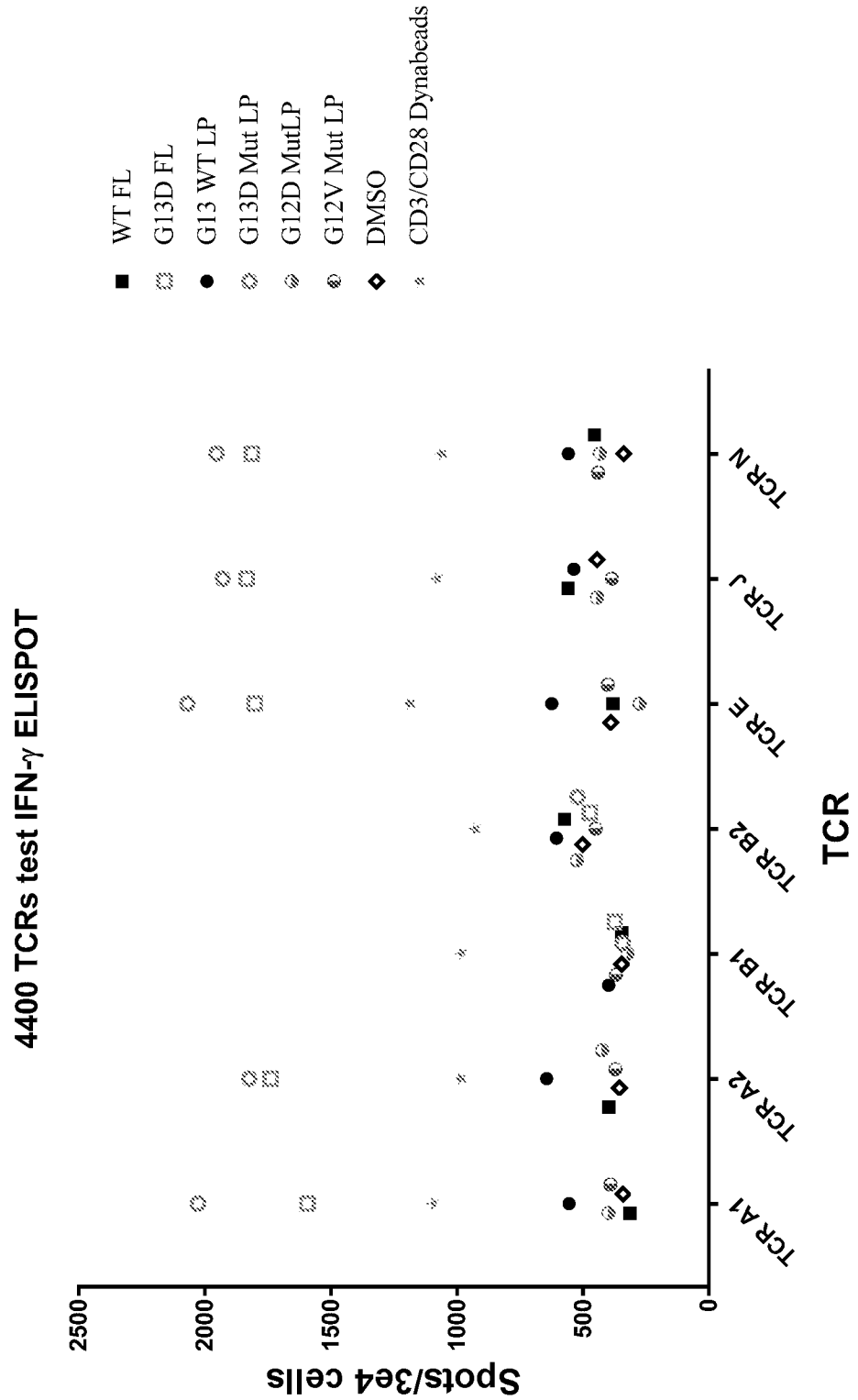


Fig. 6

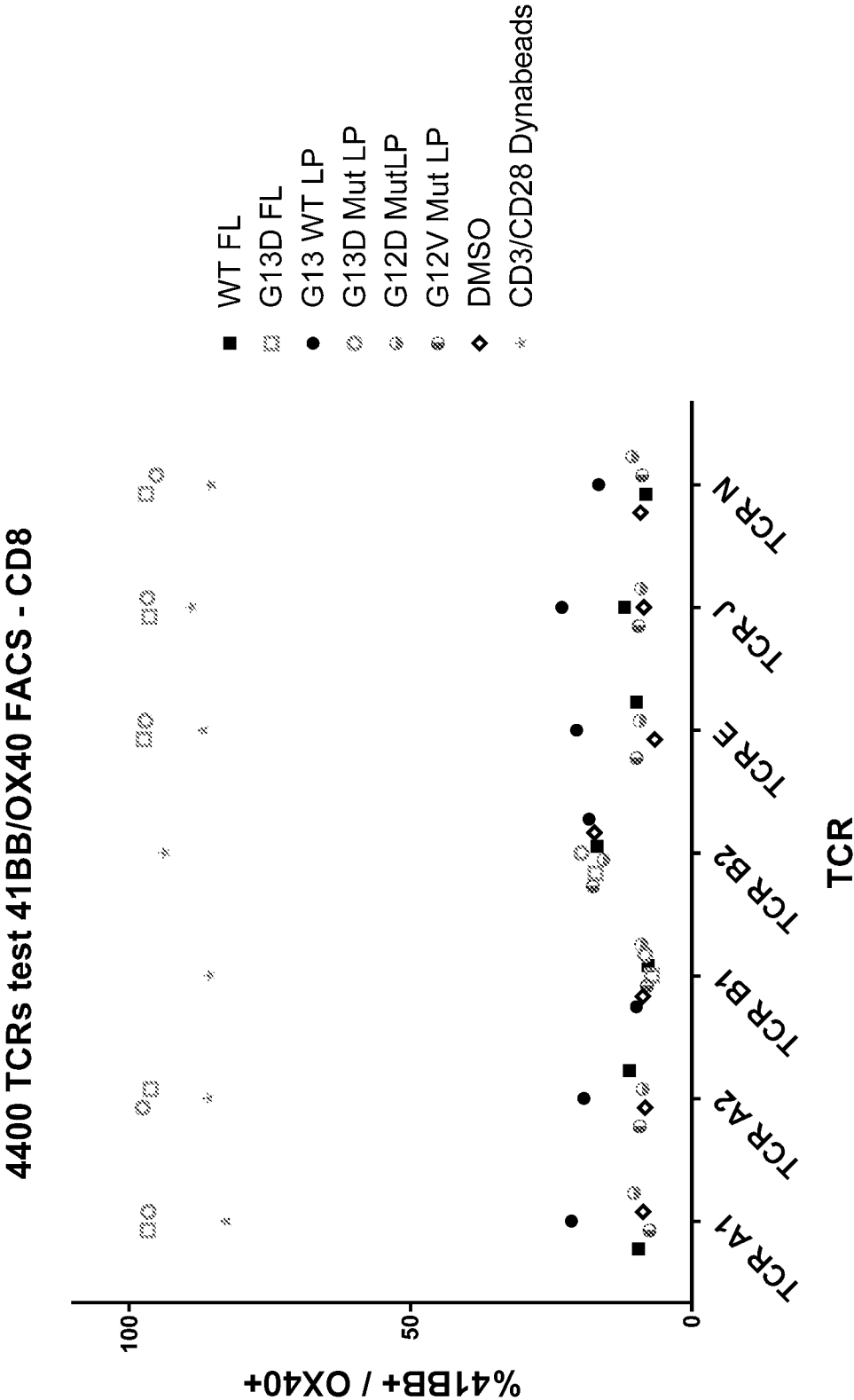


Fig. 7A

4400 TCRs test 41BB/OX40 FACS - CD4

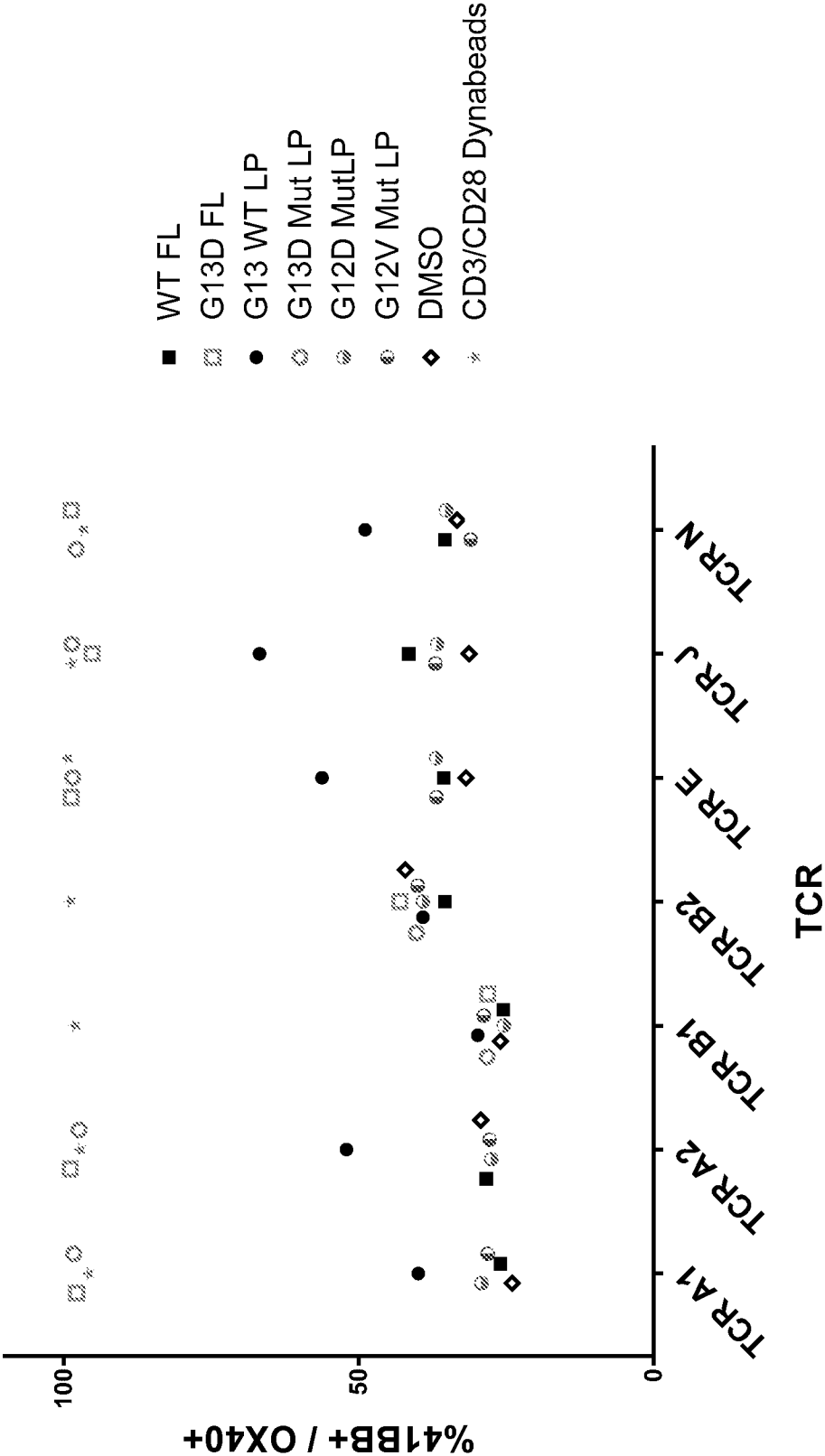
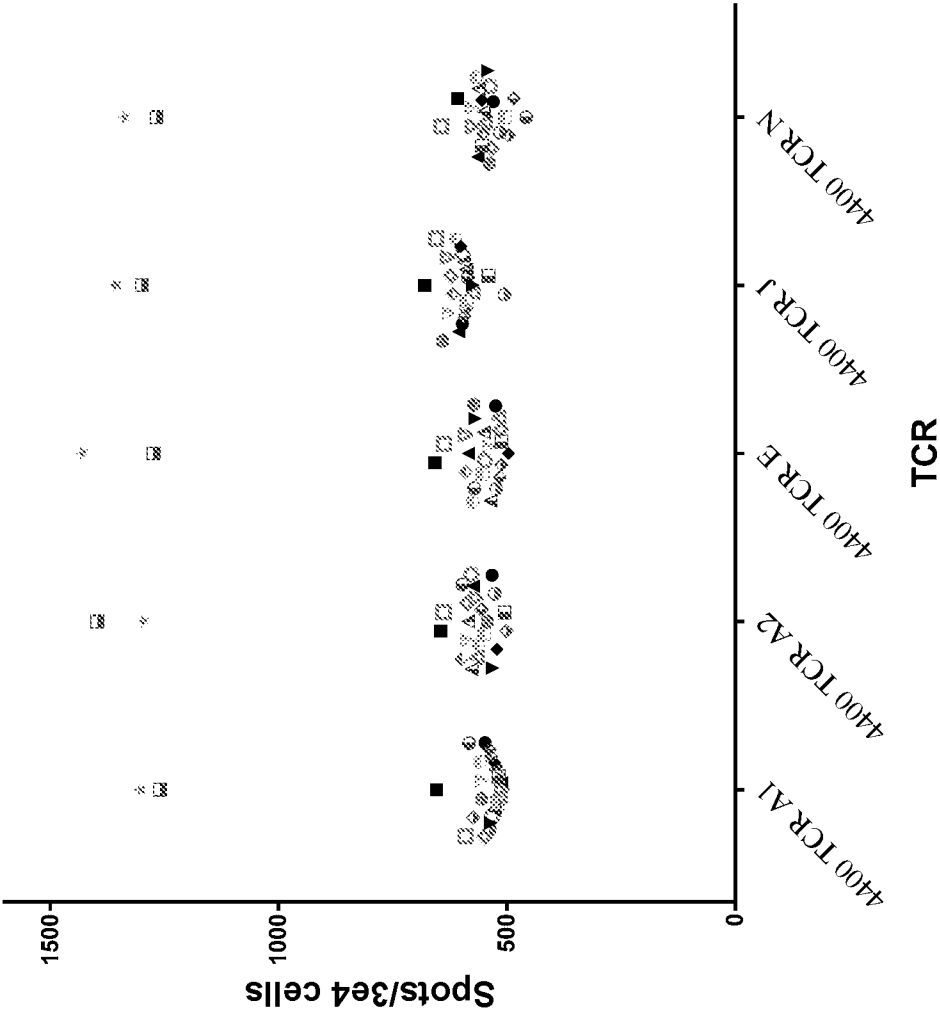


Fig. 7B

4400 TCRs MHC-II test IFN- γ ELISPOT



- DRA*01:01 + DRB1*03:01
- DRA*01:01 + DRB1*11:01
- ◐ DRA*01:01 + DRB1*11:04
- ◑ DRA*01:01 + DRB1*07:01
- ◒ DRA*01:01 + DRB1*14:01
- ◆ DRA*01:01 + DRB3*01:01
- ◈ DRA*01:01 + DRB3*03:01
- ◉ DRA*01:01 + DRB3*02:02
- ◊ DRA*01:01 + DRB3*02:01
- ◌ DRA*01:01 + DRB4*01:01
- ▲ DPA1*02:01:01 + DPB1*01:01
- ◈ DPA1*02:01:01 + DPB1*04:02:01
- ▲ DPA1*03:03 + DPB1*01:01
- ▲ DPA1*03:03 + DPB1*04:02:01
- ▼ DPA1*01:03:01 + DPB1*03:01:01
- ◈ DPA1*01:03:01 + DPB1*04:01:01
- ◈ DPA1*01:03:01 + DPB1*06:01:01
- DQA1*01:02 + DQB1*02:01
- ◈ DQA1*01:02 + DQB1*05:02
- ◈ DQA1*05:01 + DQB1*02:01
- ◈ DQA1*05:01 + DQB1*05:02
- ◈ DQA1*05:01 + DQB1*03:01
- ◈ HEKno trans
- ✱ CD3/CD28 Dynabeads

Fig. 8

4400 TCRs MHC-II test 41BB/OX40 - CD4

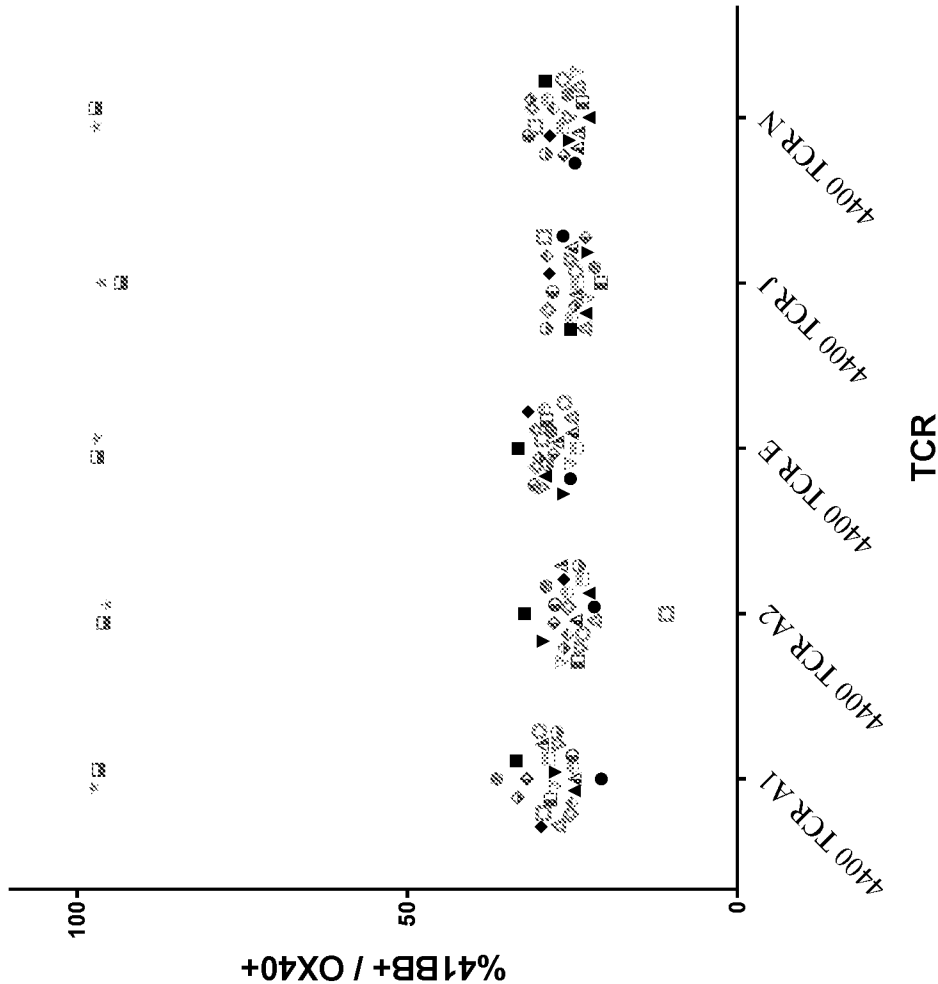


Fig. 9

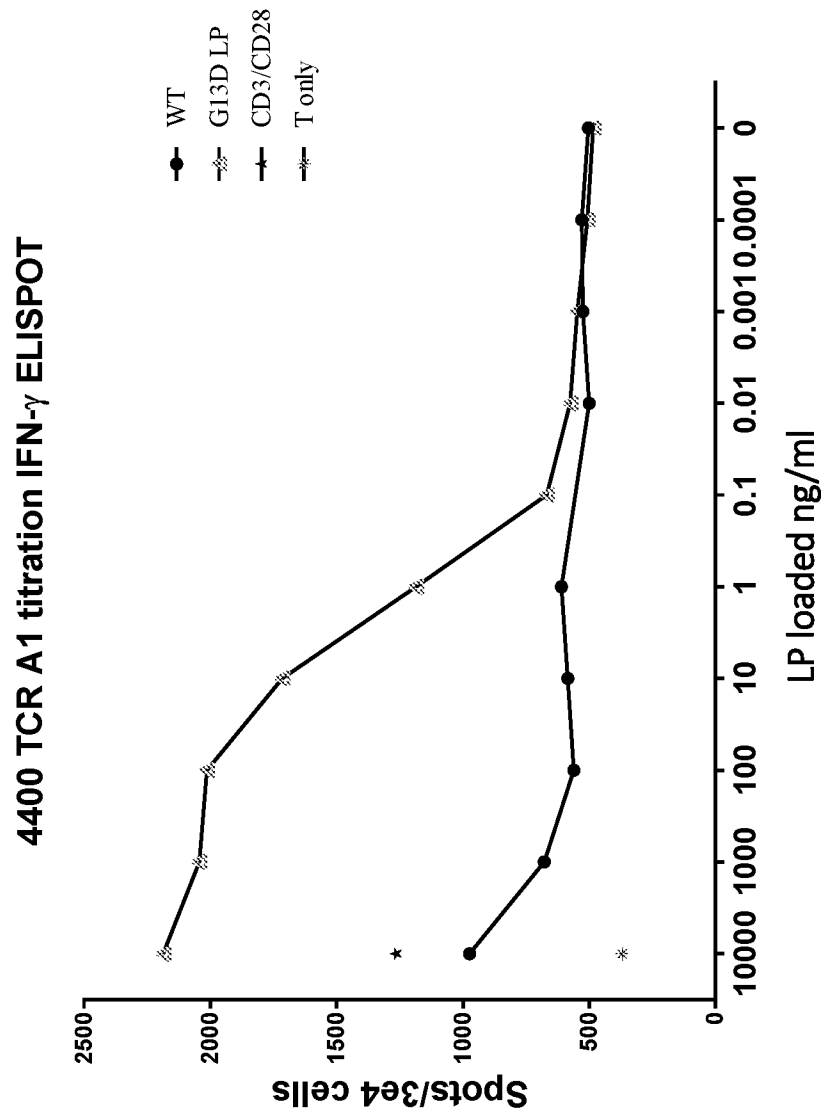


Fig. 10A

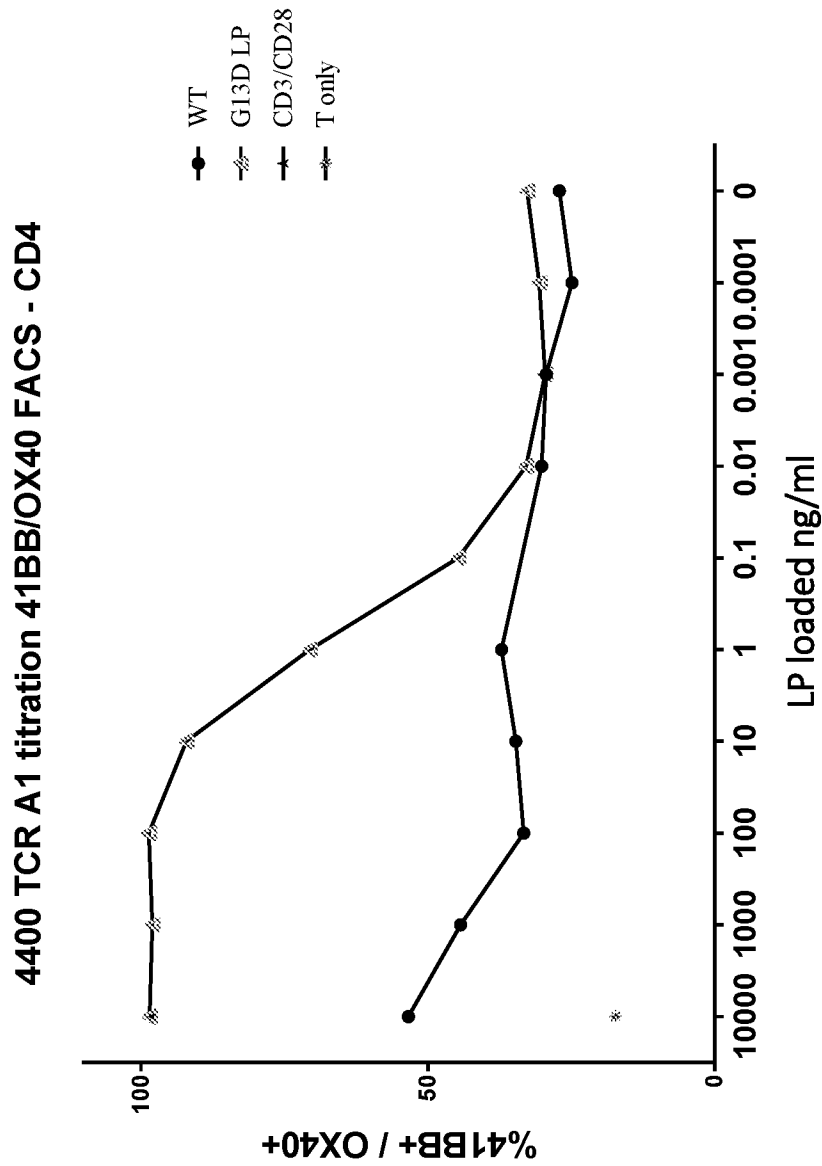


Fig. 10B

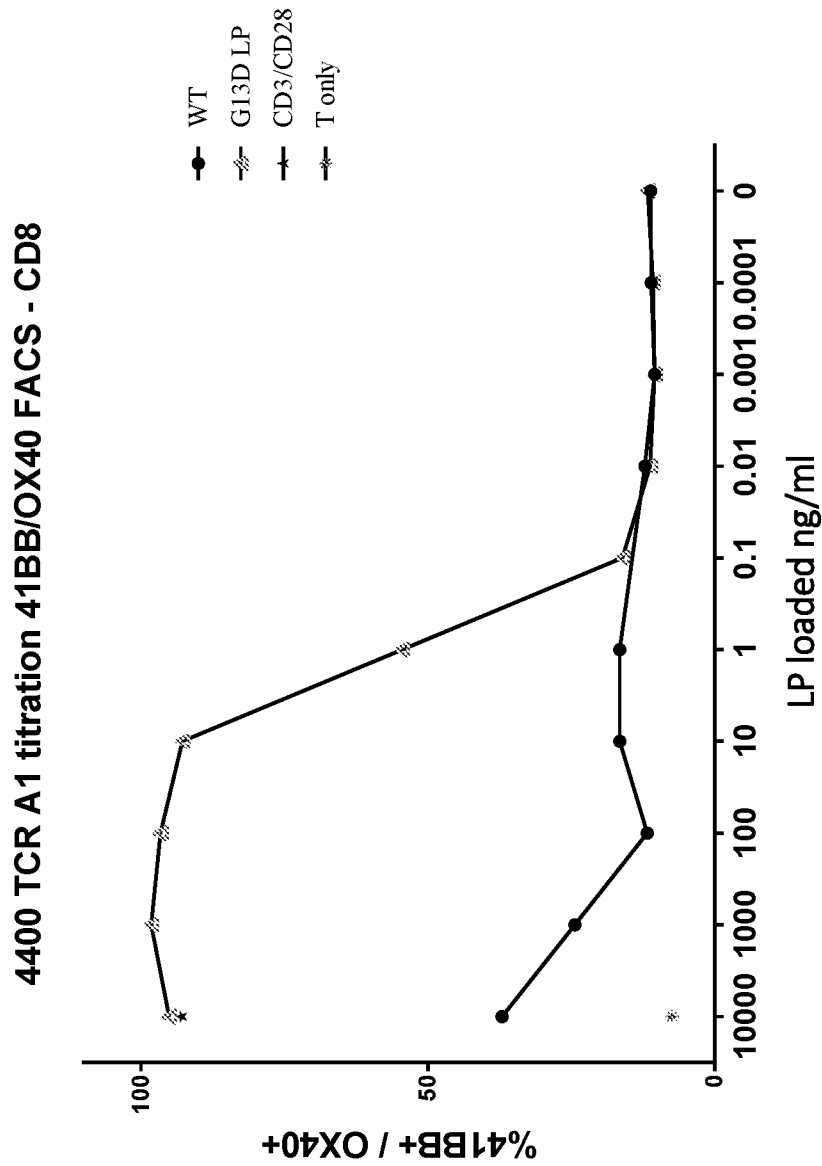


Fig. 10C

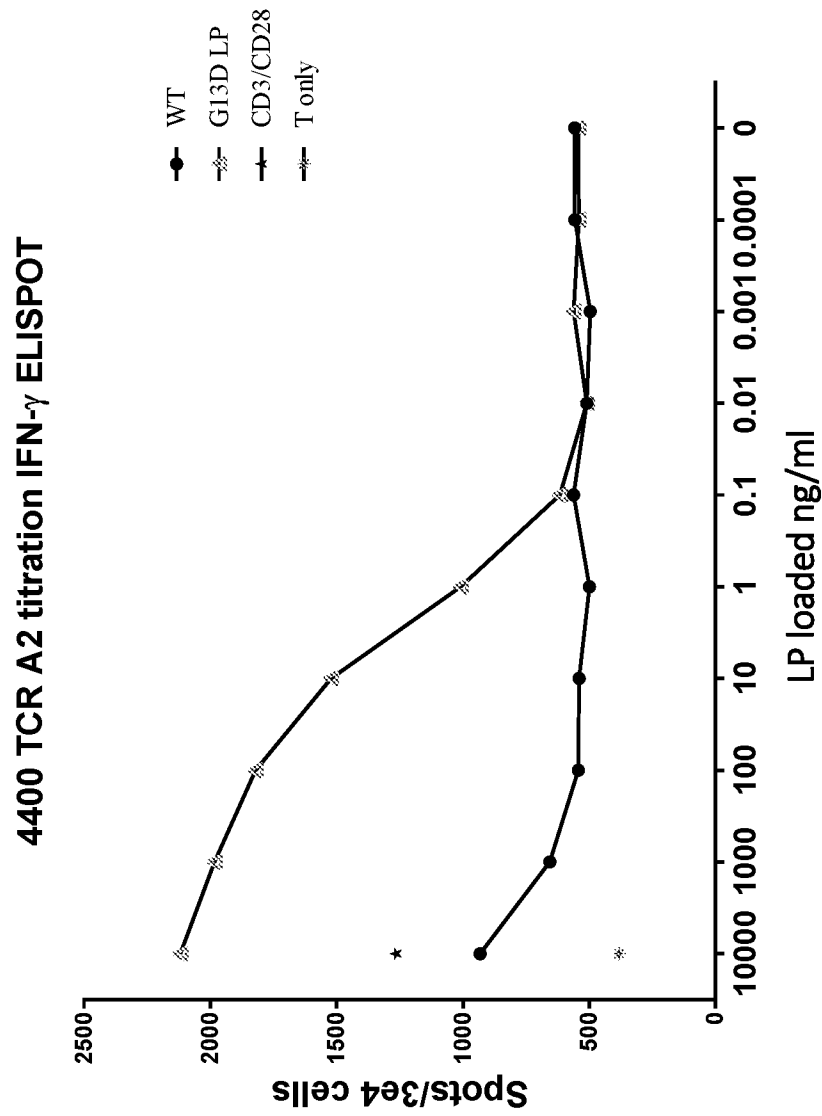


Fig. 11A

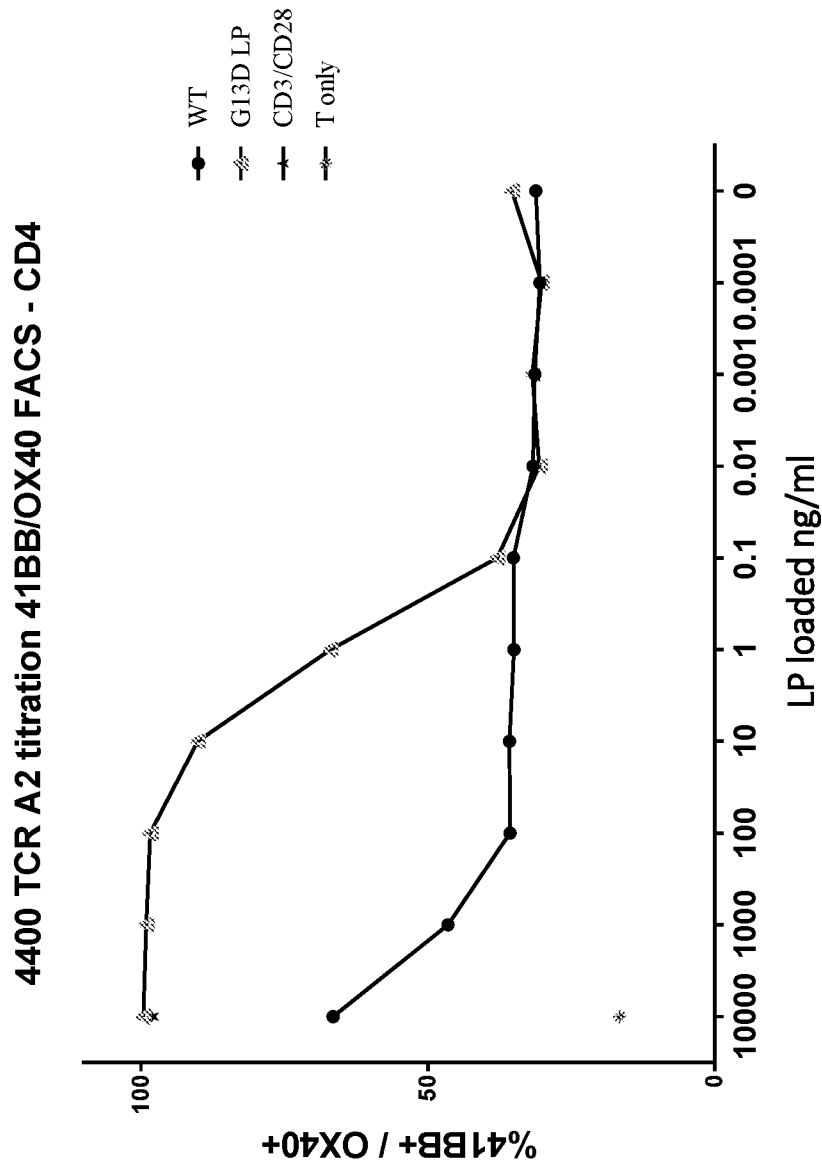


Fig. 11B

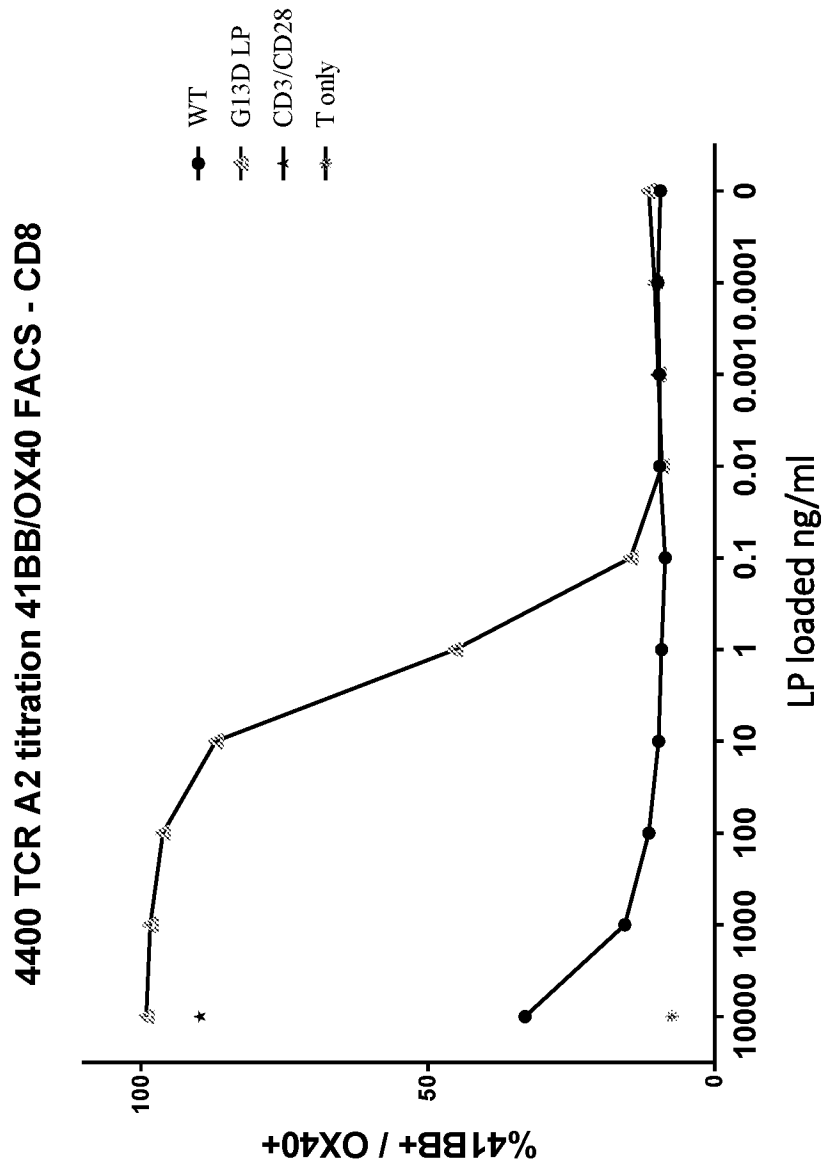


Fig. 11C

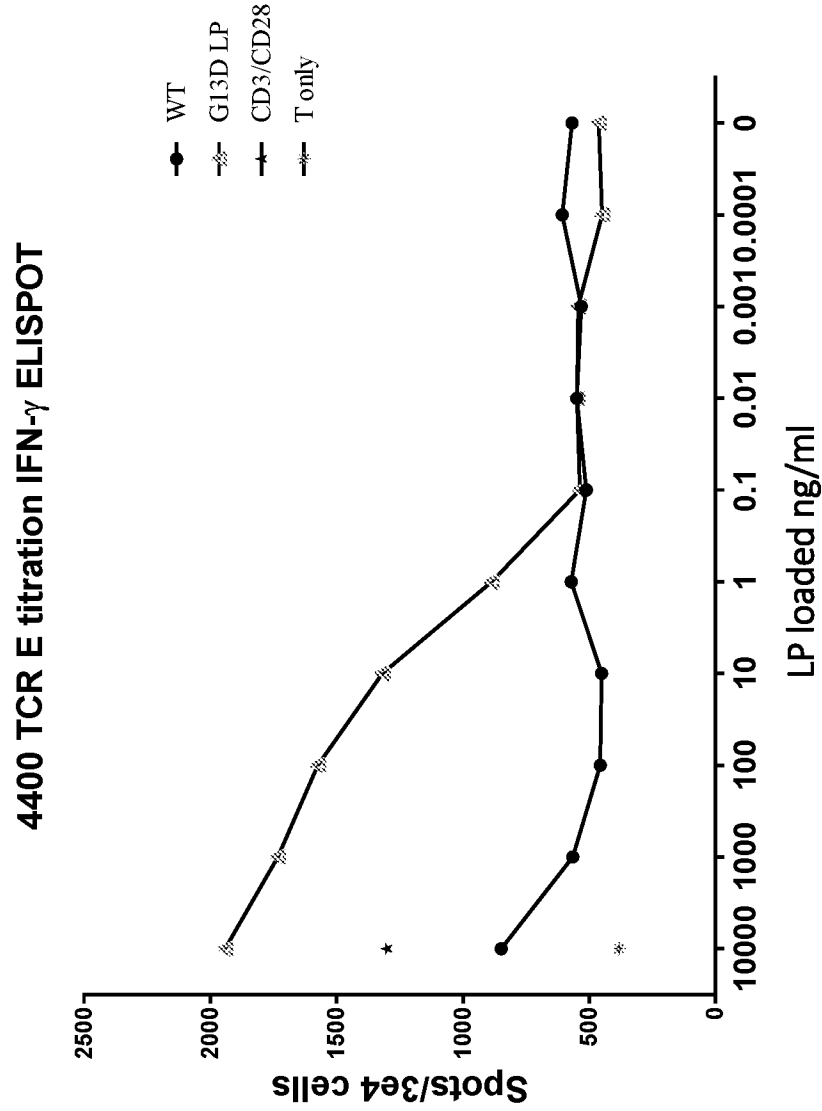


Fig. 12A

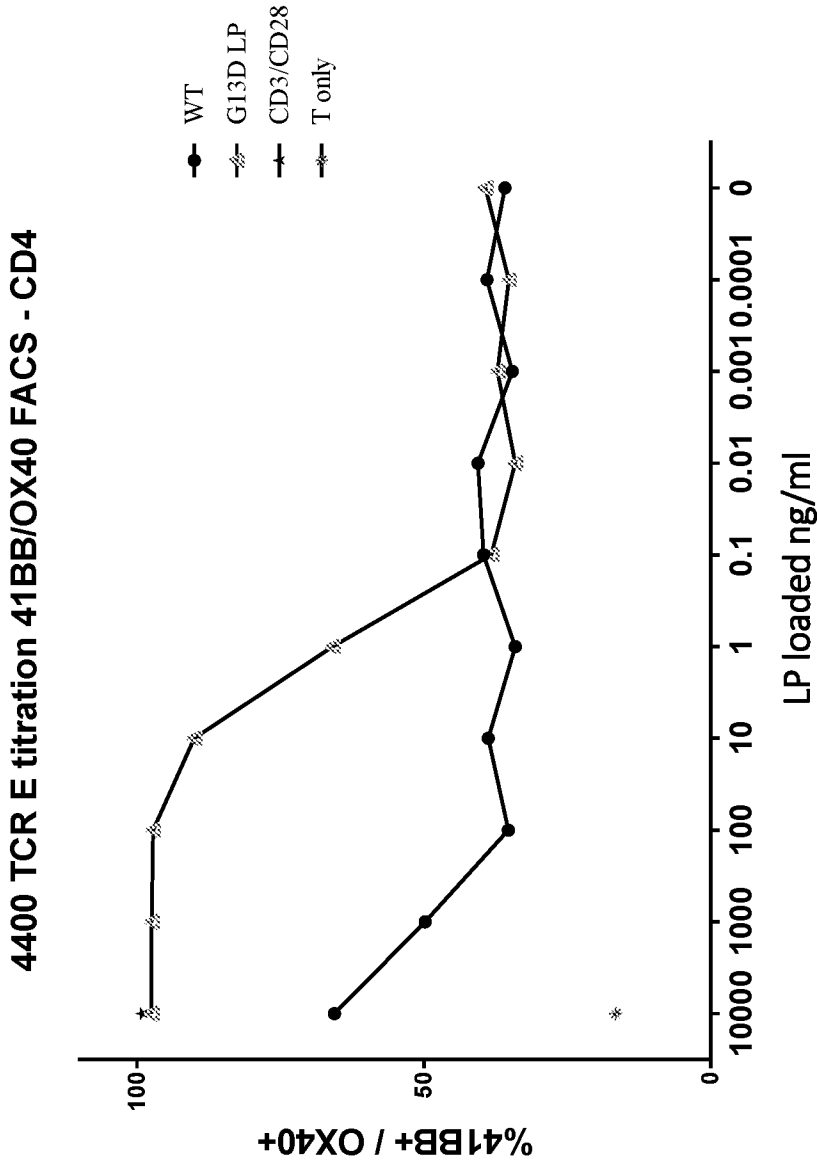


Fig. 12B

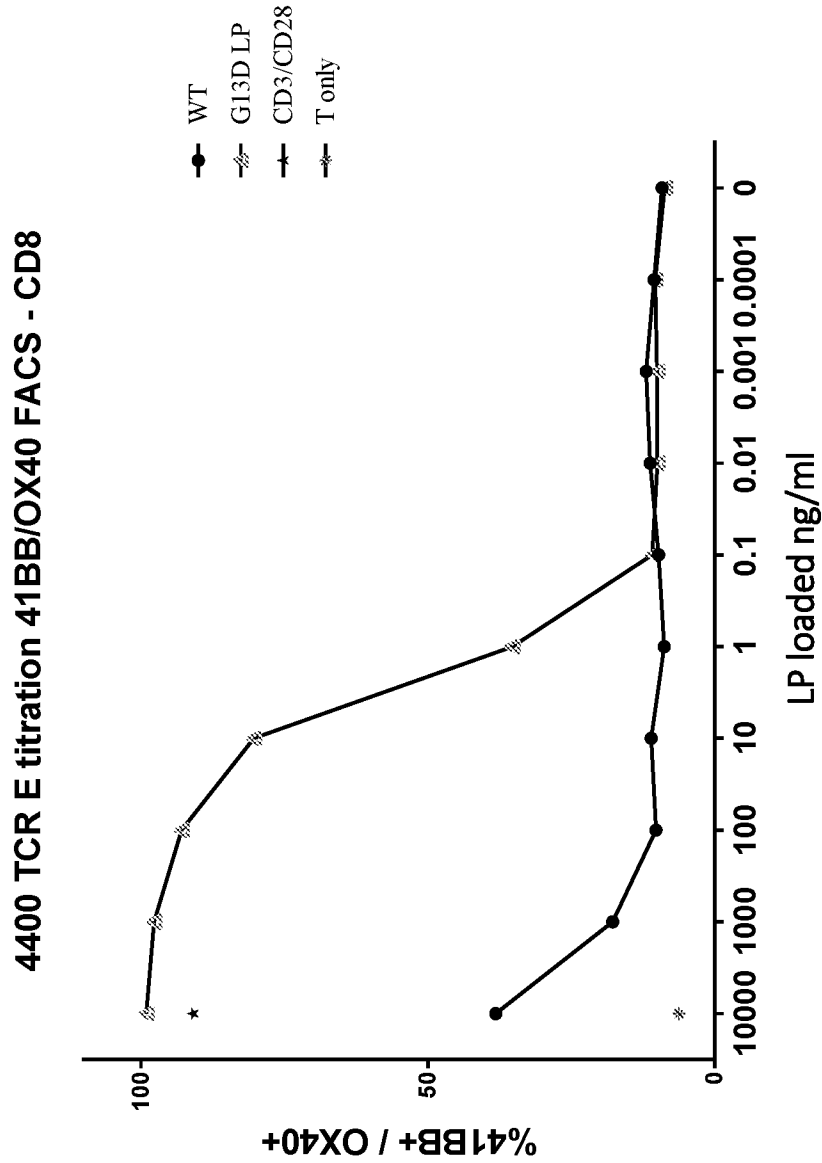


Fig. 12C

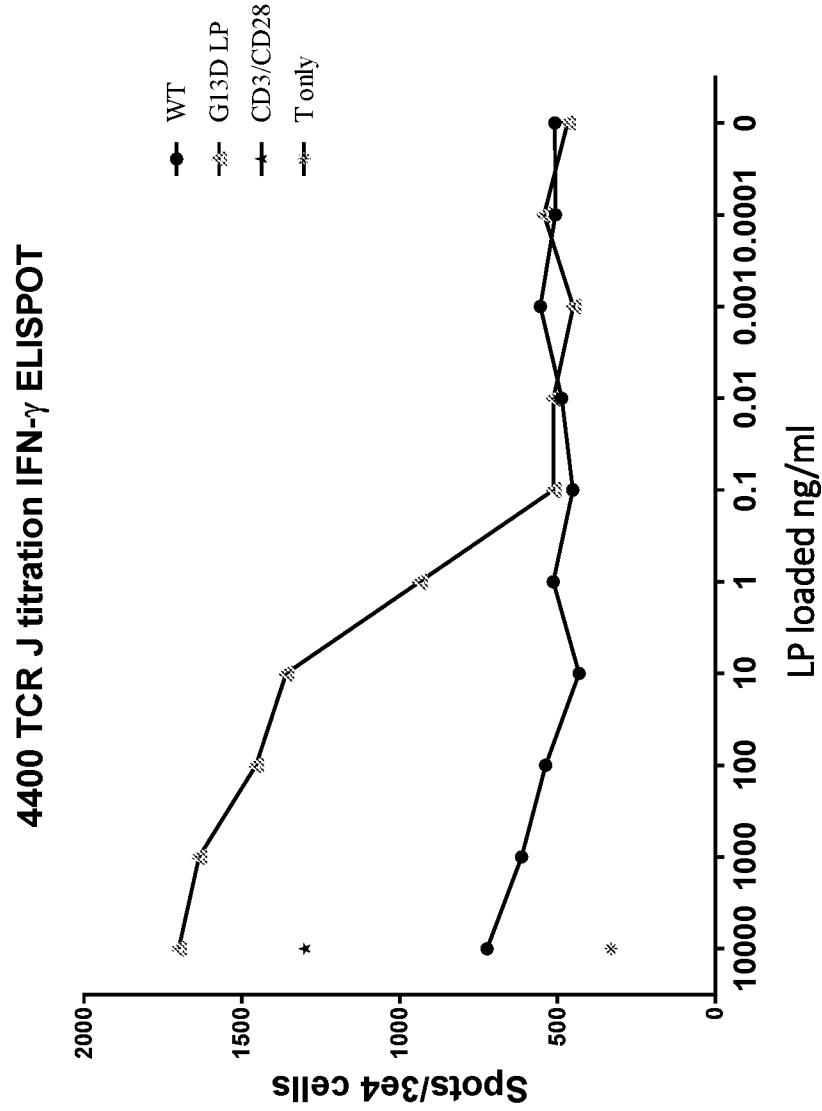


Fig. 13A

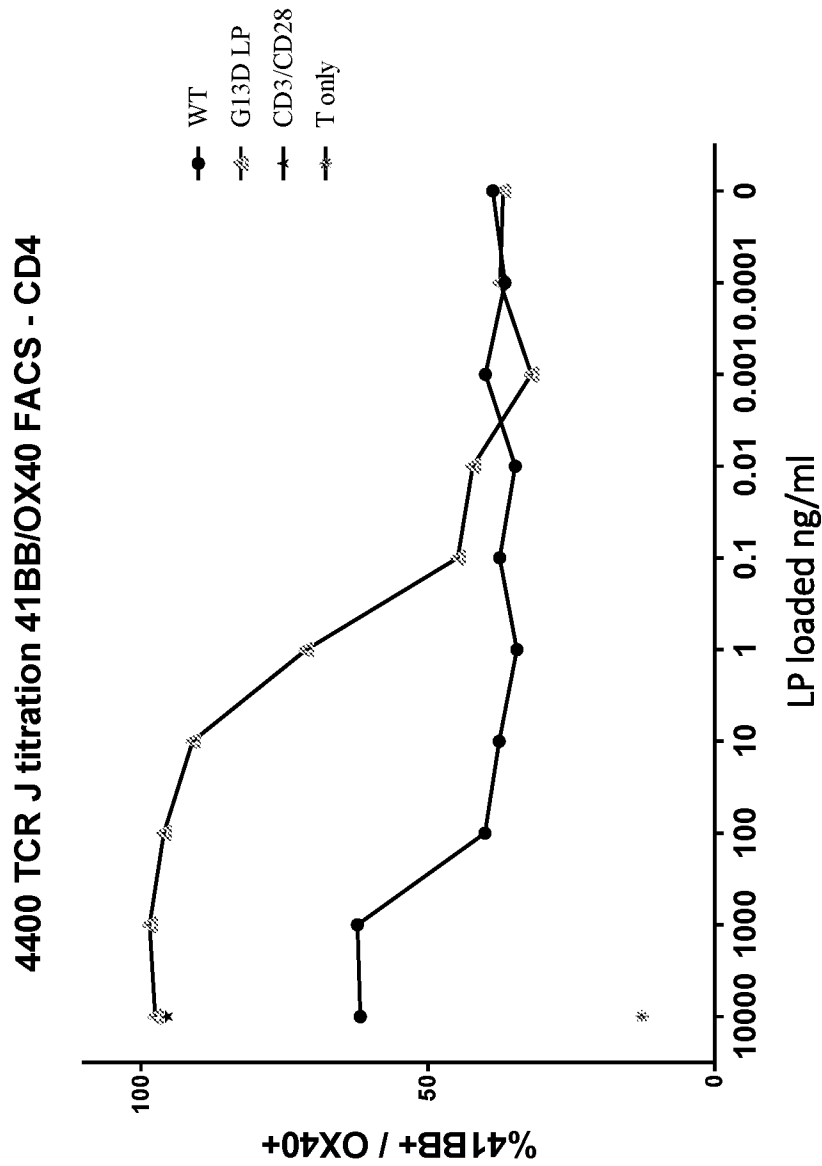


Fig. 13B

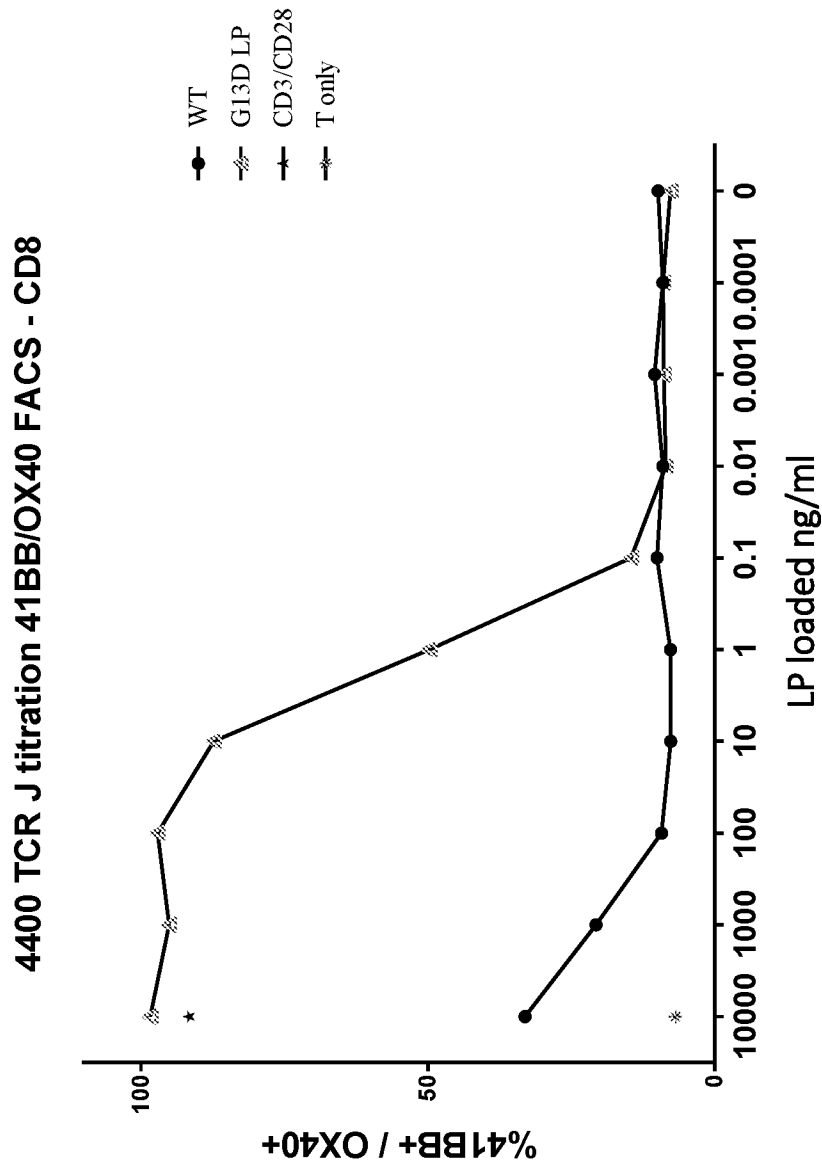


Fig. 13C

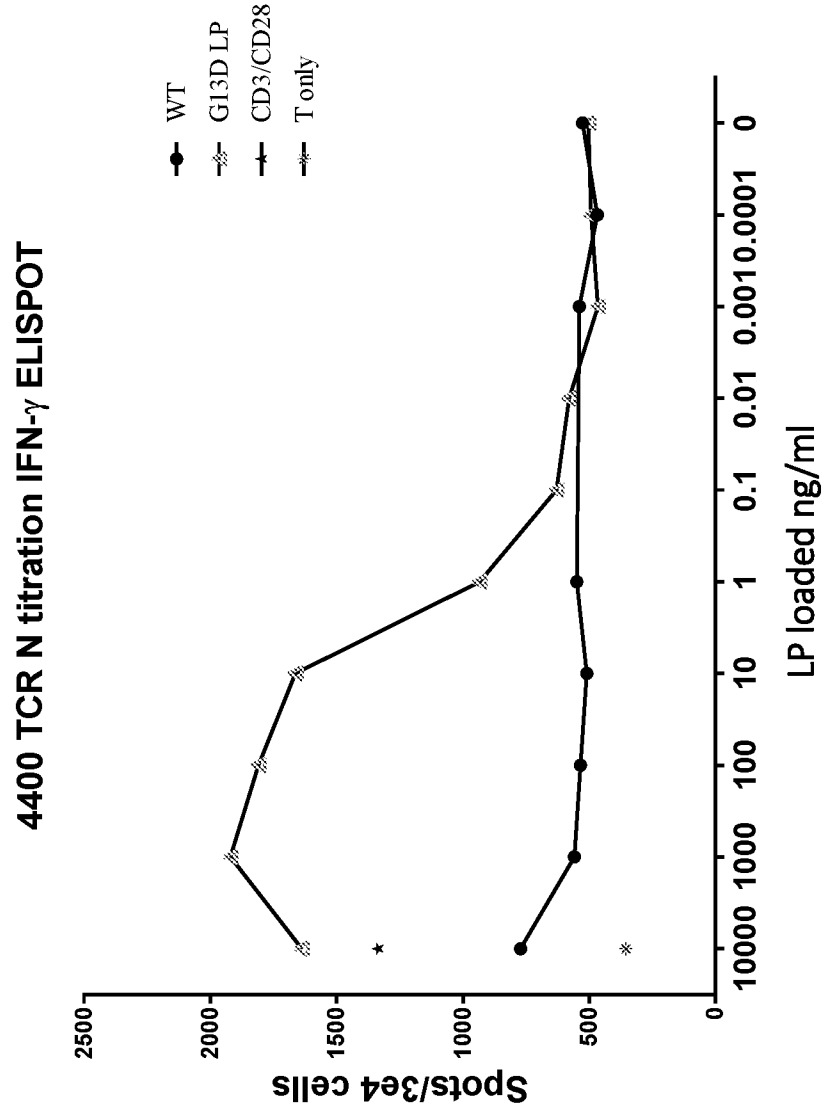


Fig. 14A

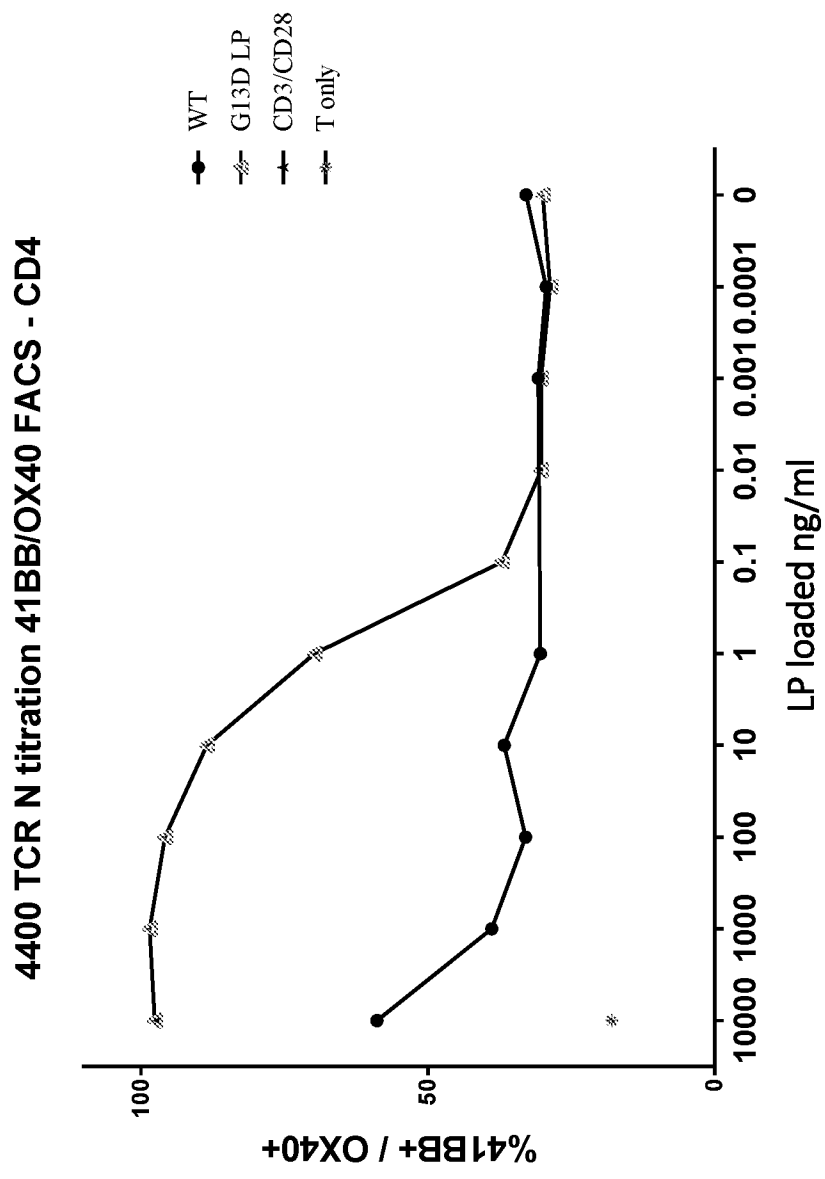


Fig. 14B

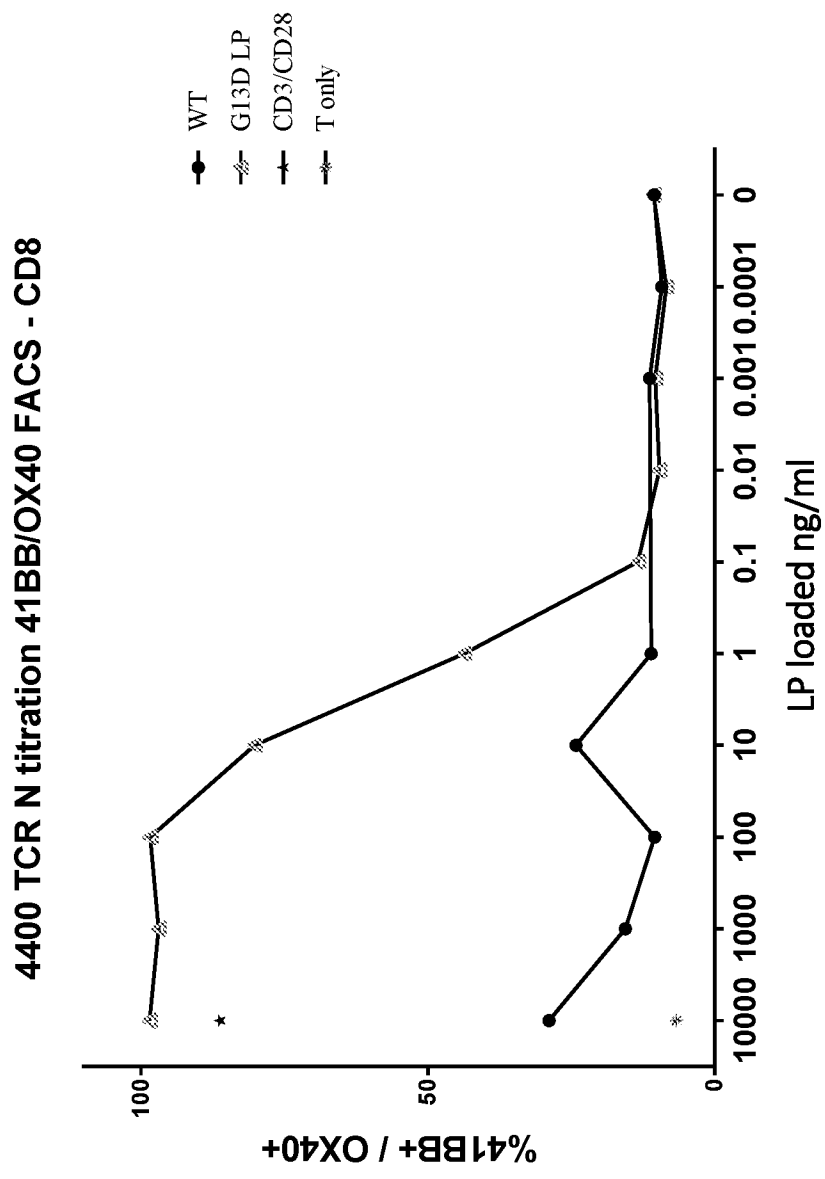


Fig. 14C

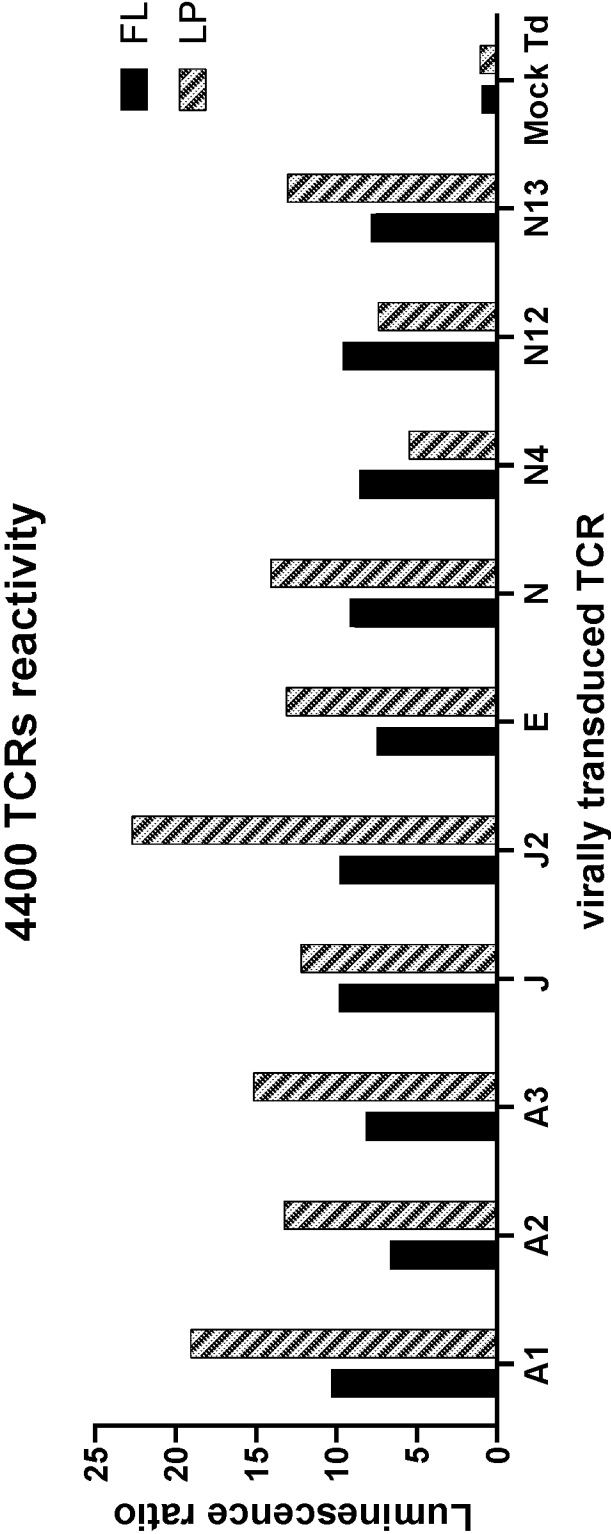


Fig. 15

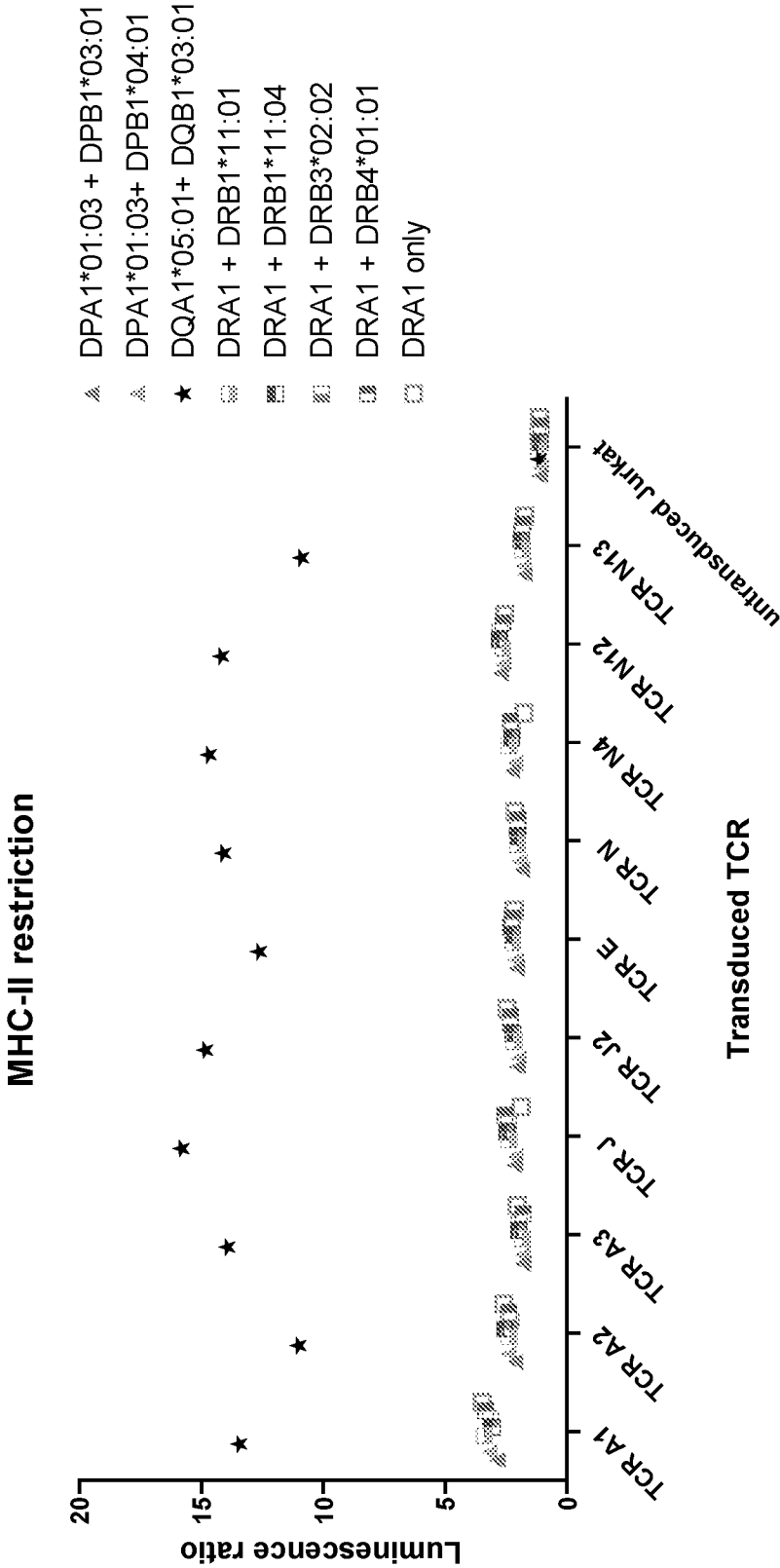


Fig. 16

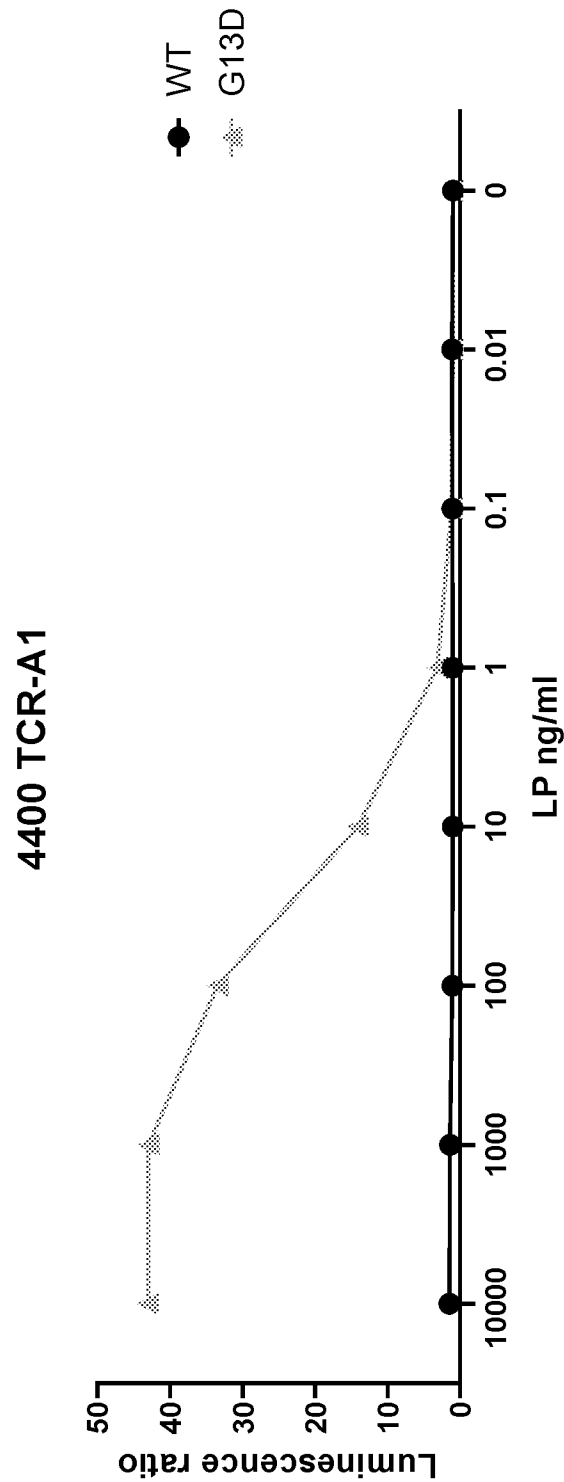


Fig. 17A

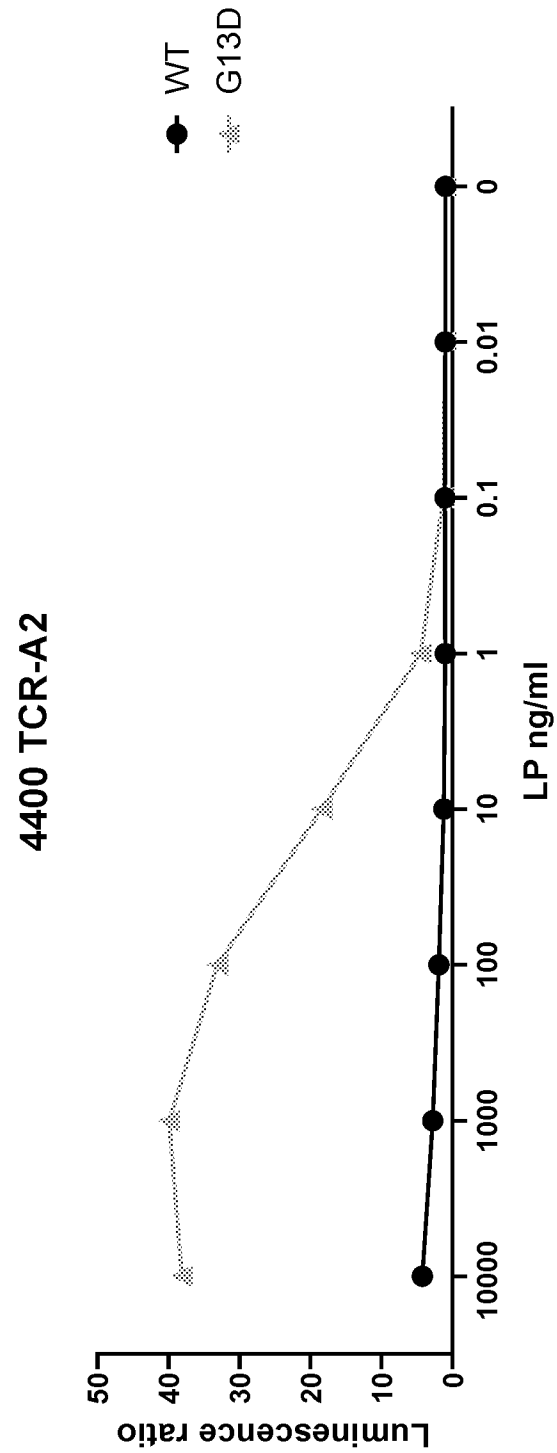


Fig. 17B

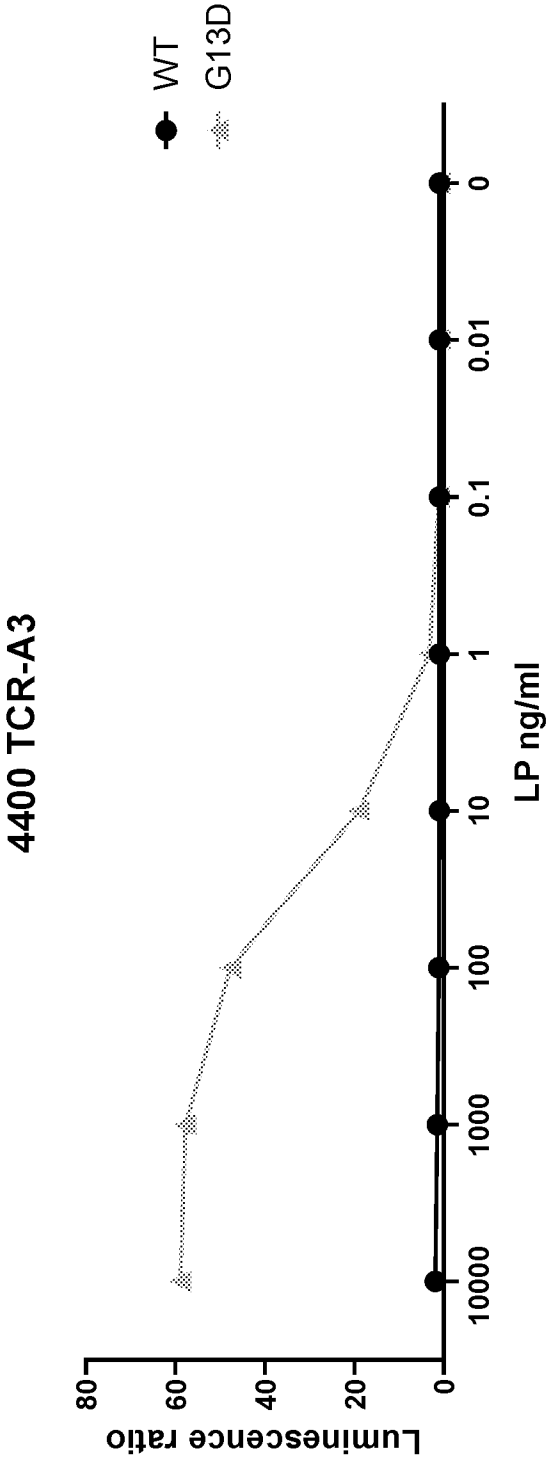


Fig. 17C

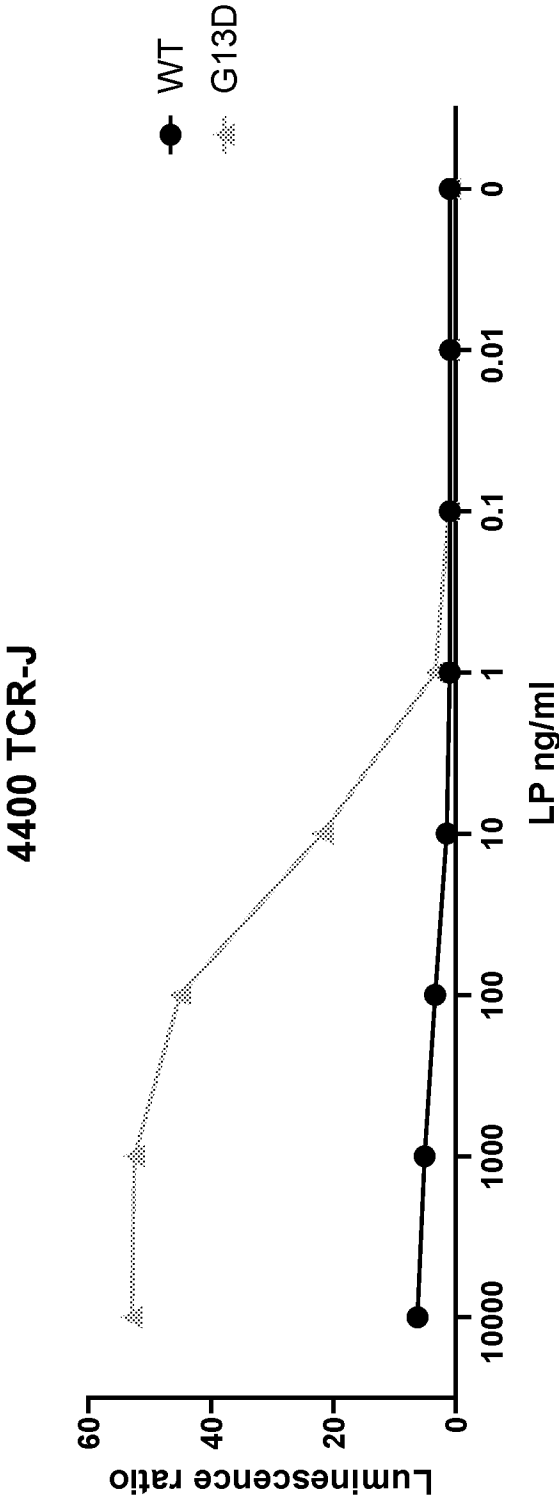


Fig. 17D

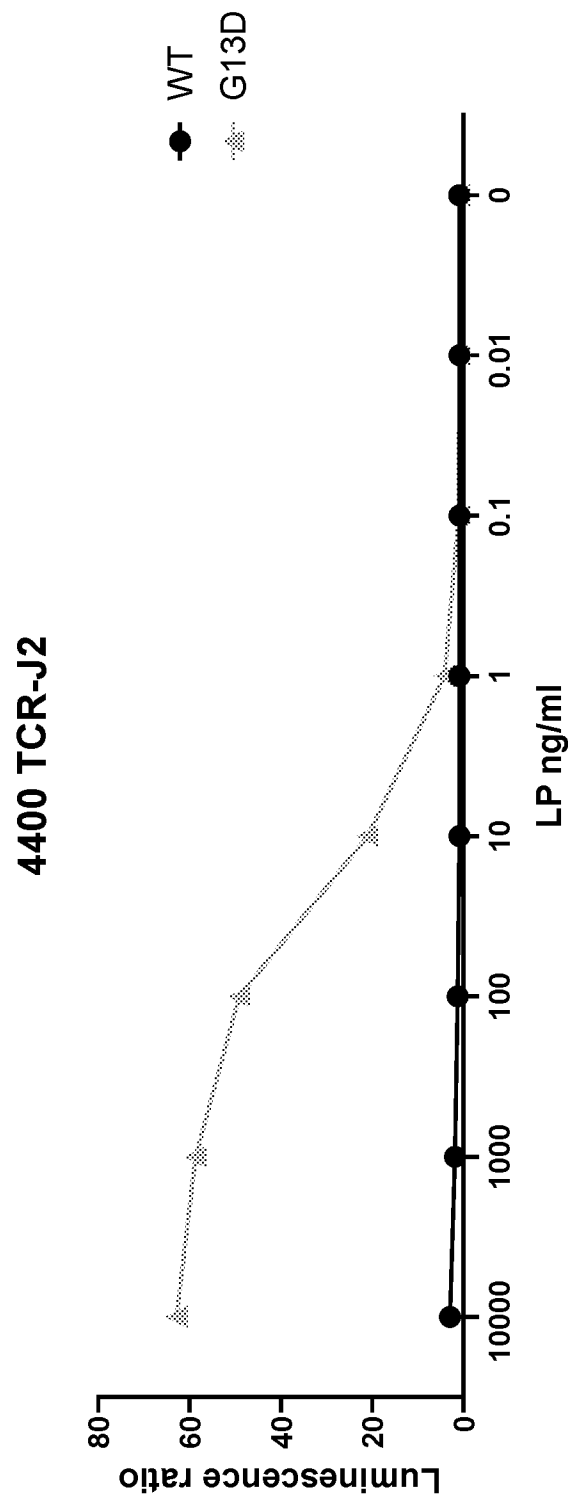


Fig. 17E

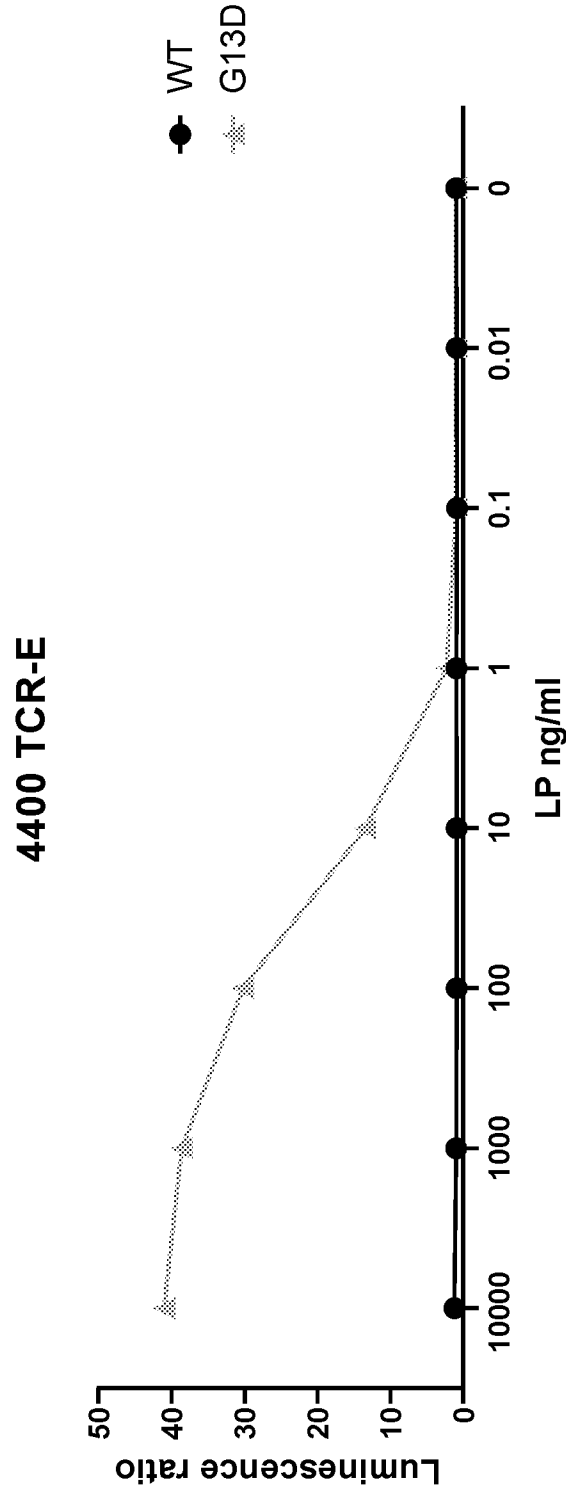


Fig. 17F

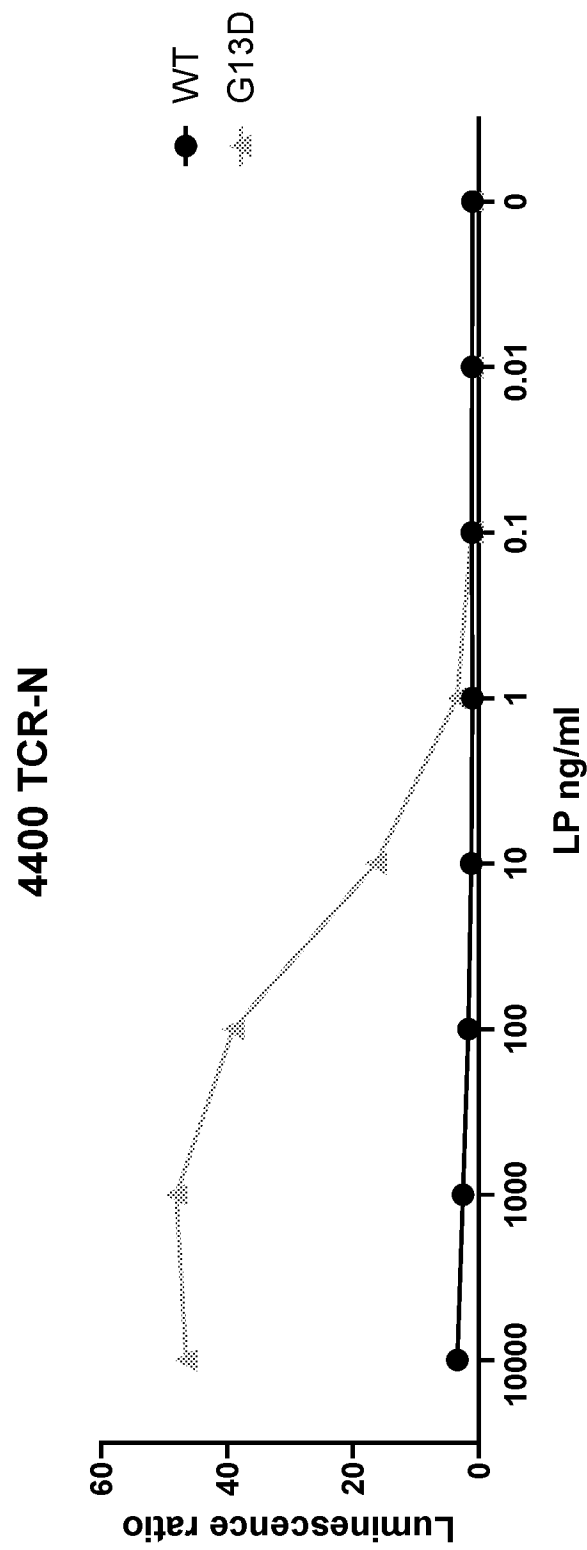


Fig. 17G

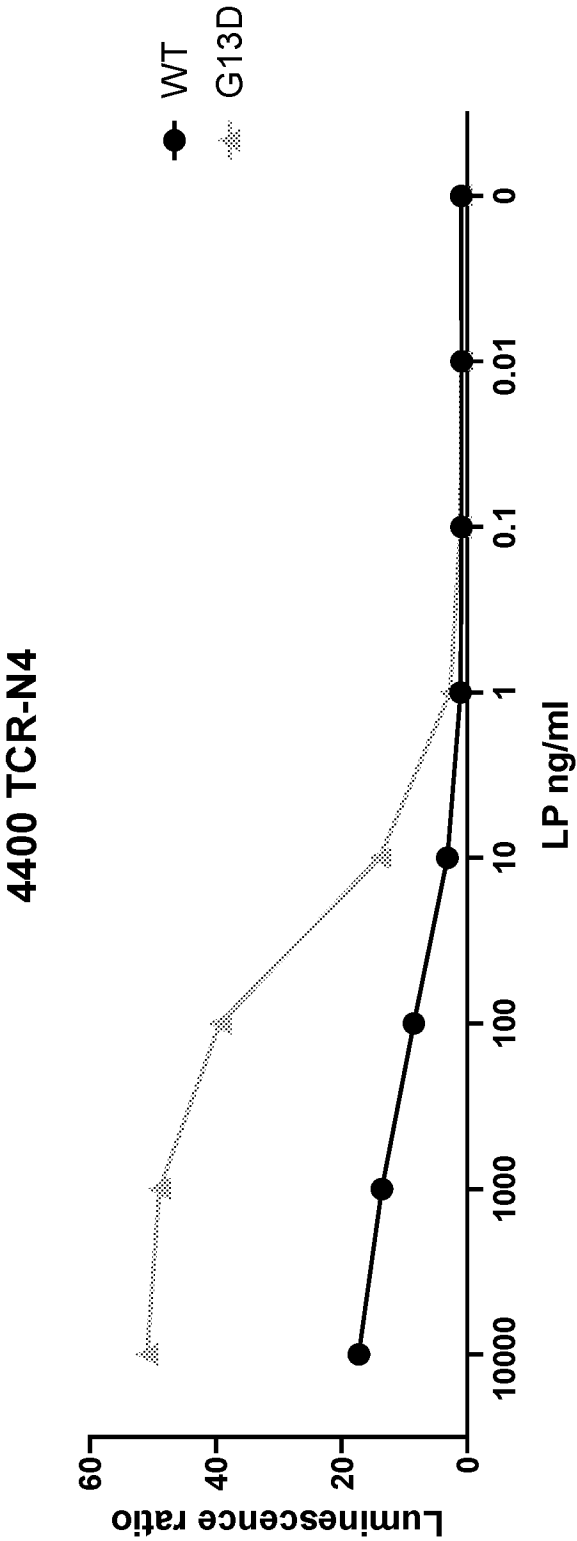


Fig. 17H

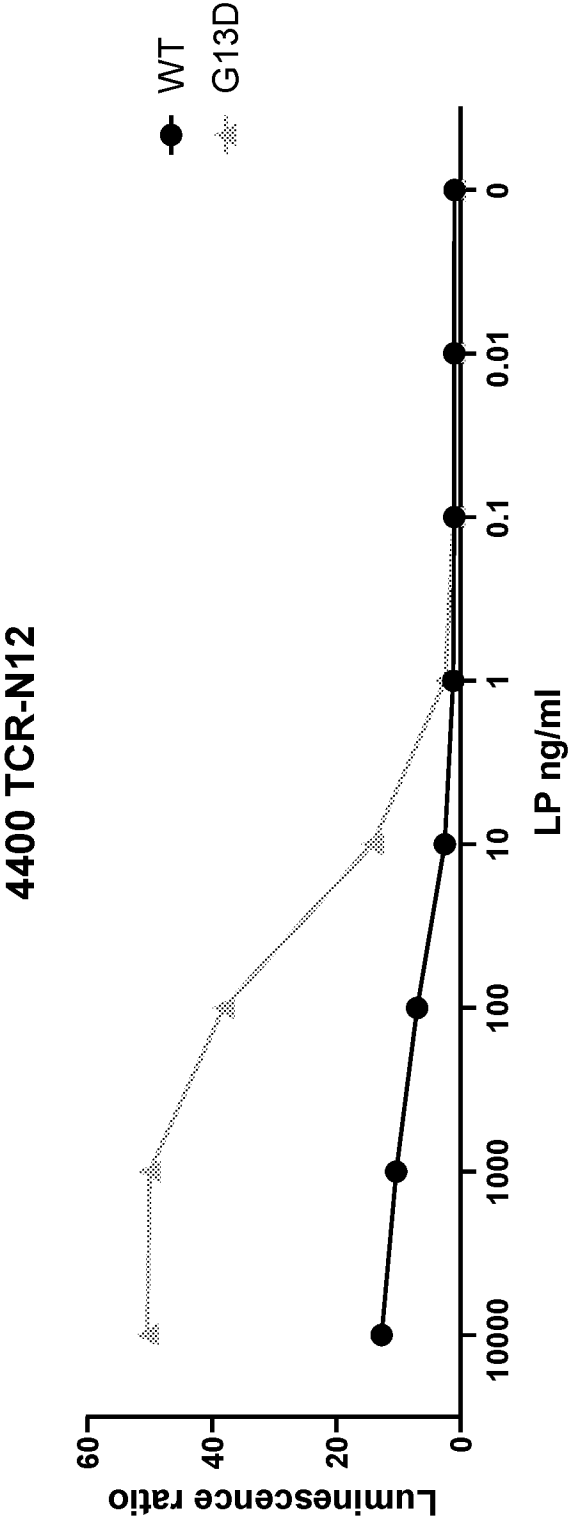


Fig. 17I

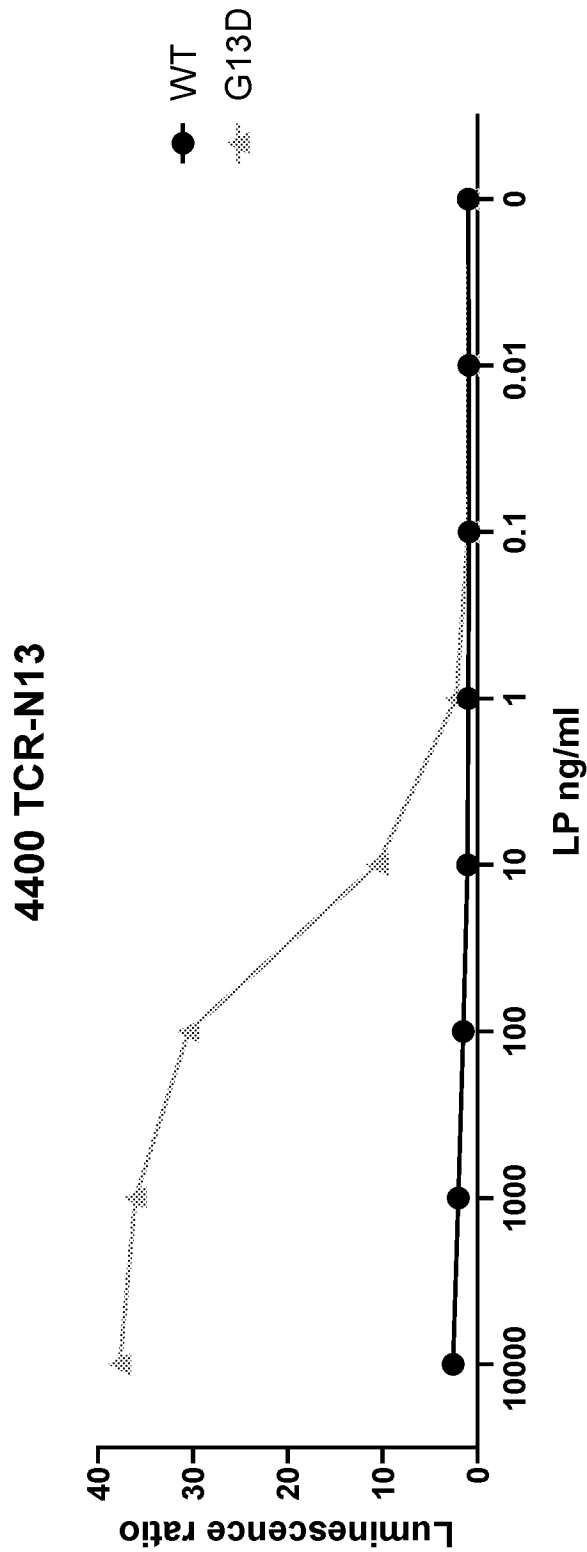


Fig. 17J

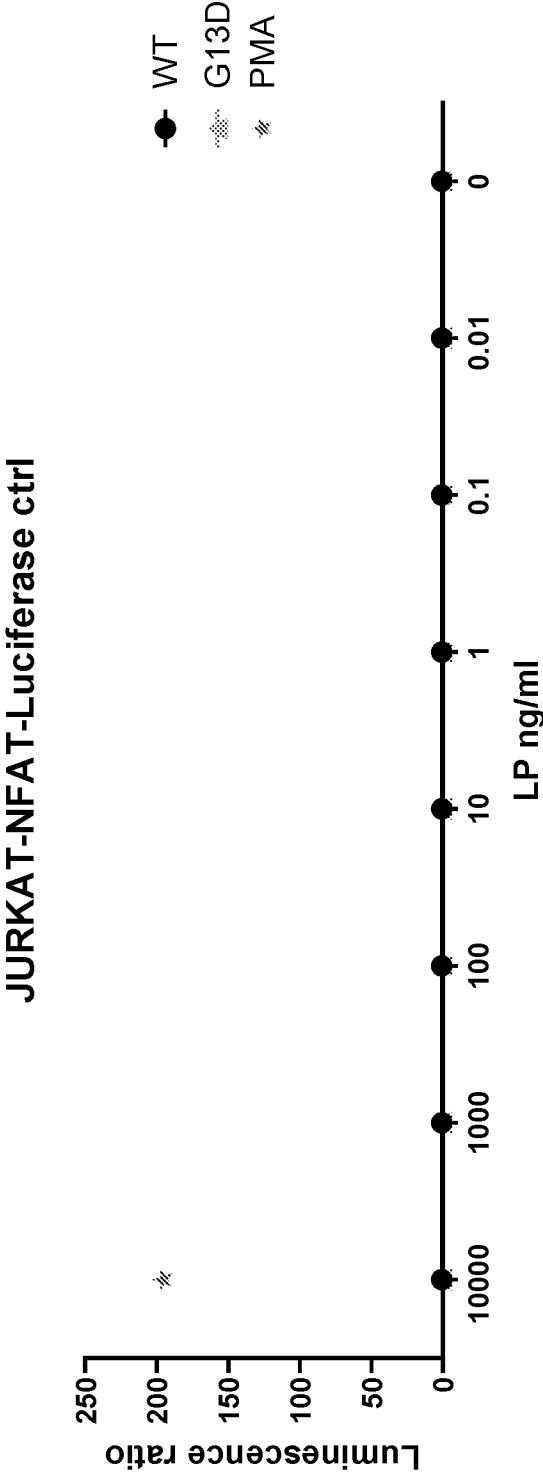


Fig. 17K

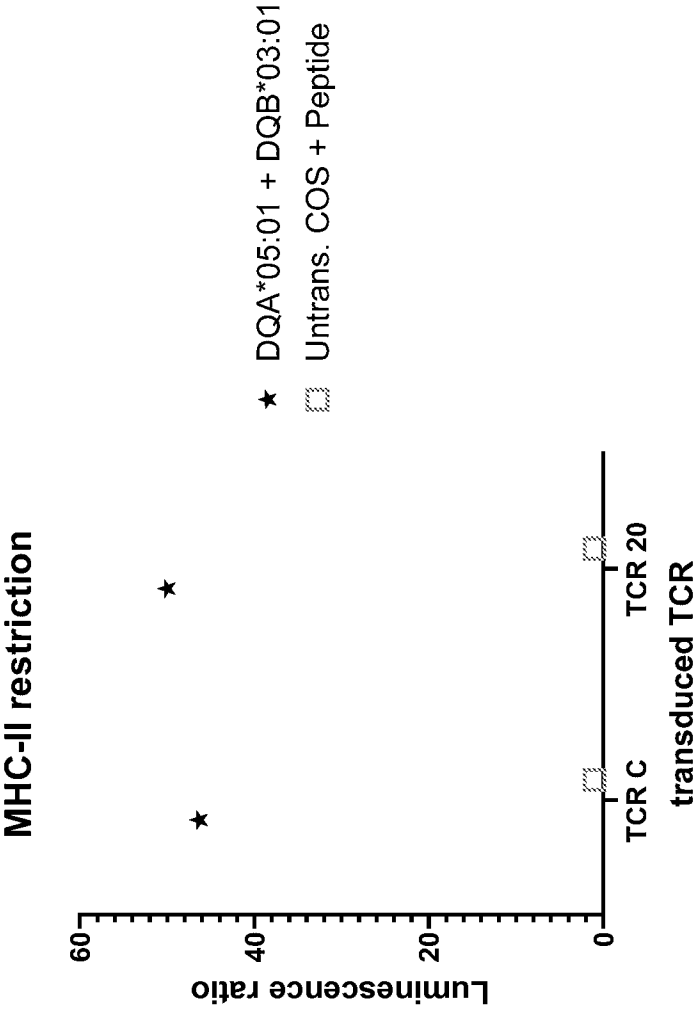


Fig. 18

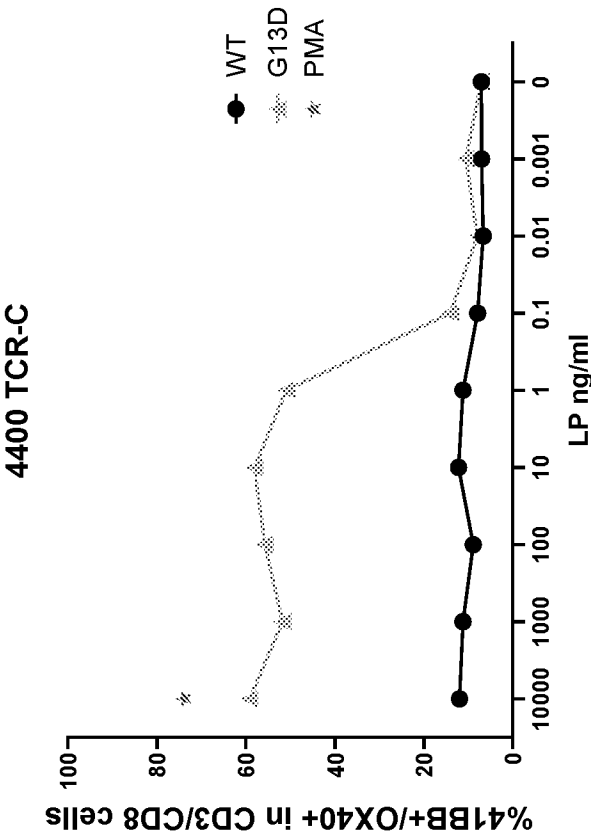


Fig. 19B

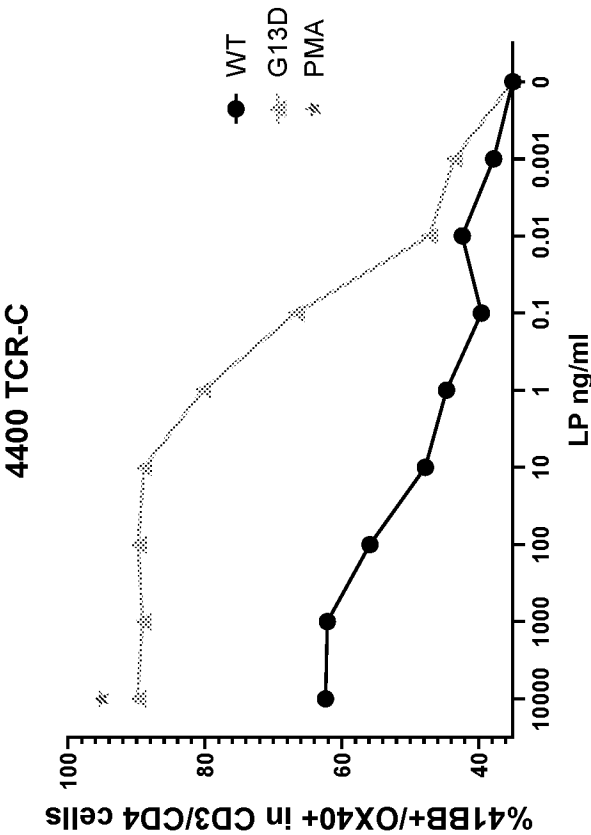


Fig. 19A

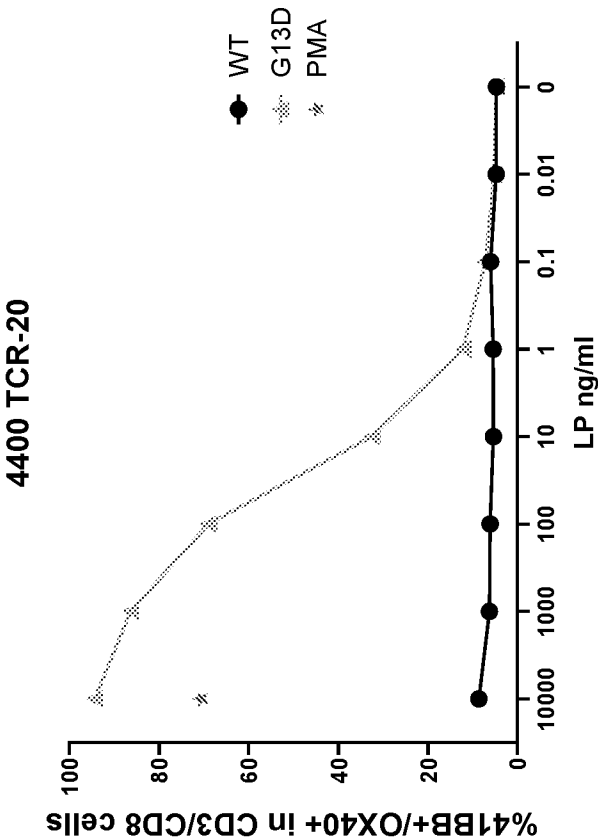


Fig. 19D

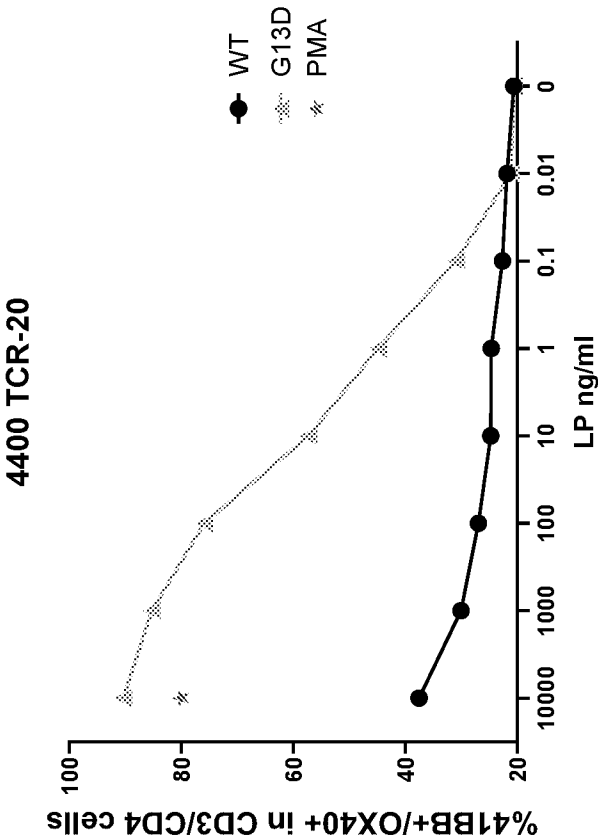


Fig. 19C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/053060

A. CLASSIFICATION OF SUBJECT MATTER INV. C07K14/725 A61K35/17 C12N5/0783 ADD. A61K35/12		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07K A61K C12N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHARITOU THEODOSIA ET AL: "Transcriptional and metabolic rewiring of colorectal cancer cells expressing the oncogenic KRASG13Dmutation", BRITISH JOURNAL OF CANCER, NATURE PUBLISHING GROUP UK, LONDON, vol. 121, no. 1, 28 May 2019 (2019-05-28), pages 37-50, XP036824511, ISSN: 0007-0920, DOI: 10.1038/S41416-019-0477-7 [retrieved on 2019-05-28] the whole document -----	2-10, 12-14, 16-18, 20-42
A	WO 2019/112941 A1 (US HEALTH [US]) 13 June 2019 (2019-06-13) the whole document -----	2-10, 12-14, 16-18, 20-42
-/--		
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 15 December 2021	Date of mailing of the international search report 14/02/2022	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Galli, Ivo	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2021/053060

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/085904 A1 (US HEALTH [US]) 2 June 2016 (2016-06-02) the whole document -----	2-10, 12-14, 16-18, 20-42
A	Rive Craig M. ET AL: "Recombinant T cell receptors specific for HLA-A*02:01-restricted neoepitopes containing KRAS codon 12 hotspot mutations", bioRxiv, 16 June 2020 (2020-06-16), pages 1-23, XP055872788, DOI: 10.1101/2020.06.15.149021 Retrieved from the Internet: URL:https://www.biorxiv.org/content/10.1101/2020.06.15.149021v1.full.pdf [retrieved on 2021-12-14] the whole document -----	2-10, 12-14, 16-18, 20-42
A	WO 2019/195492 A1 (JUNO THERAPEUTICS INC [US]; EDITAS MEDICINE INC [US]) 10 October 2019 (2019-10-10) sequences 15-16 -----	10,14,18
A	SHIOTA MITSUTAKA ET AL: "Somatic Mosaicism for a NRAS Mutation Associates with Disparate Clinical Features in RAS-associated Leukoproliferative Disease: a Report of Two Cases", J. CLIN. IMMUNOL., vol. 35, 1 January 2015 (2015-01-01), pages 454-458, XP055873329, the whole document -----	2-10, 12-14, 16-18, 20-42
X,P	WO 2021/163434 A1 (US HEALTH [US]) 19 August 2021 (2021-08-19) the whole document -----	2-10, 12-14, 16-18, 20-42
X,P	WO 2021/170684 A1 (OBLIQUE THERAPEUTICS AB [SE]) 2 September 2021 (2021-09-02) figure 1 -----	2-10, 12-14, 16-18, 20-42

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/053060

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/053060

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: **1, 11, 15, 19 (completely); 2-10, 12-14, 18, 20-42 (partially)**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:
1-42 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-42 (partially)

A TCR against RAS G13D; corresponding isolated proteins and chain pairs, coding nucleic acids, host cells and populations thereof; methods of making the host cells and of producing the TCR; pharmaceutical compositions, medical uses, method of detecting cancer.
Concerning clone A1 (tables 5-6)

2-12. claims: 1-42 (partially)

Same as (1), but concerning clones A2, E, J, N, A3, J2, N4, N12, N13, C and #20 from tables 5-6.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1, 11, 15, 19(completely); 2-10, 12-14, 18, 20-42(partially)

Pursuant to Rule 6.3(a) PCT the definition of the matter for which protection is sought shall be in terms of the technical features of the invention. Claim 1 does not contain technical features: it defines the scope of the claim purely by reference to the problem to be solved, ie finding TCRs against RAS G13D. See also PCT Guideline 5.04 - claim 1 does not contain functional limitations: it concerns a result to be achieved, which involves inventive step. The claim is circular and impossible to search meaningfully, as are its dependent claims that do not fully define the TCR chain pairs.

The same applies in part to claims 2, 9, 12, 13 - insofar as only one of the two members of the TCR chain pairs is defined. These claims (and their dependent claims that do not fully define the TCR chain pairs) cannot be meaningfully searched.

Finally, pursuant to Art.

6 PCT the claims shall be precise and concise. Claims 11, 15, 19 manifestly do not meet this requirement, see also PCT Guideline 5.42 and A5.42[2]. They so lack conciseness that a focused, meaningful search is impossible.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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